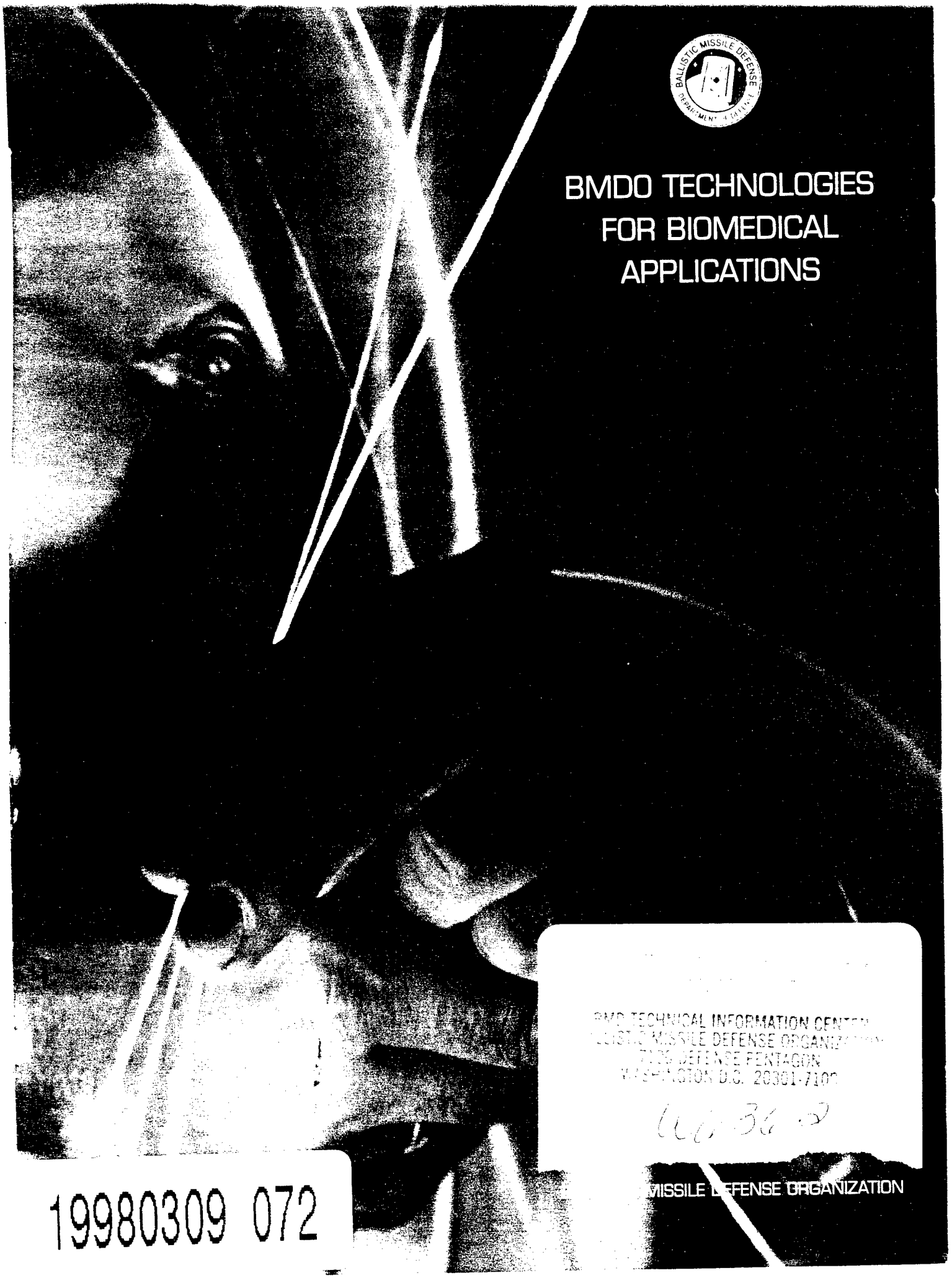

BMDO TECHNOLOGIES FOR BIOMEDICAL APPLICATIONS

BALLISTIC MISSILE DEFENSE ORGANIZATION

The Ballistic Missile Defense Organization is dedicated to state-of-the-art technology development, and continues to support defense-critical innovations that also have potential outside the military sector. Whether in materials, sensors, optics, electronics, or communications, BMDO maintains a record of excellence in moving technology advances into the mainstream, where all can sample the benefits of our national investment in defense.

For more information about technologies, laboratories, or companies featured in this report, please contact:

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c/o the National Technology Transfer Center
Washington Operations
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Abstract: In 1996, BMDO and the National Technology Transfer Center/Washington Operations (NTTC/WO) published a special report intitled "BMDO Technology Applications in Biomedicine". With an emphasis on biomedical and biotechnical areas, the report detailed more than 60 technology stories that sprang from BMDO support through the SBIR program, the STTR program, the IS&T program and the TA program. This 1997 report again highlight advances in biomedical applications of BMDO technology, covering 32 stories in image processing, optical biopsy, laser treatments, information storage and networks, and biological analyses, among other topics.

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BMDO TECHNOLOGIES FOR BIOMEDICAL APPLICATIONS

Ballistic Missile Defense Organization

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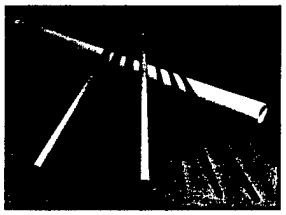

CHAPTER 3 - INTERVENTION TECHNOLOGIES

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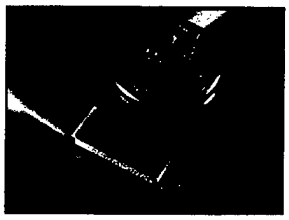
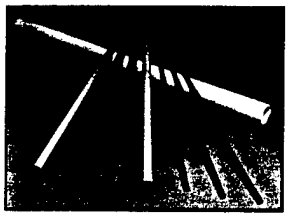
INTRODUCTION

In 1996, the Ballistic Missile Defense Organization (BMDO) and the National Technology Transfer Center/Washington Operations (NTTC/WO) published a special report entitled *BMDO Technology Applications in Biomedicine*. With an emphasis on biomedical and biotechnical areas, this report detailed more than 60 technology stories that sprang from BMDO support through the Small Business Innovation Research (SBIR) program, the Small Business Technology Transfer (STTR) program, the Innovative Science and Technology (IS&T) program, and the Technology Applications (TA) program. This year, we are again highlighting advances in biomedical applications of BMDO technology, covering 32 stories in image processing, optical biopsy, laser treatments, information storage and networks, and biological analyses, among other topics.



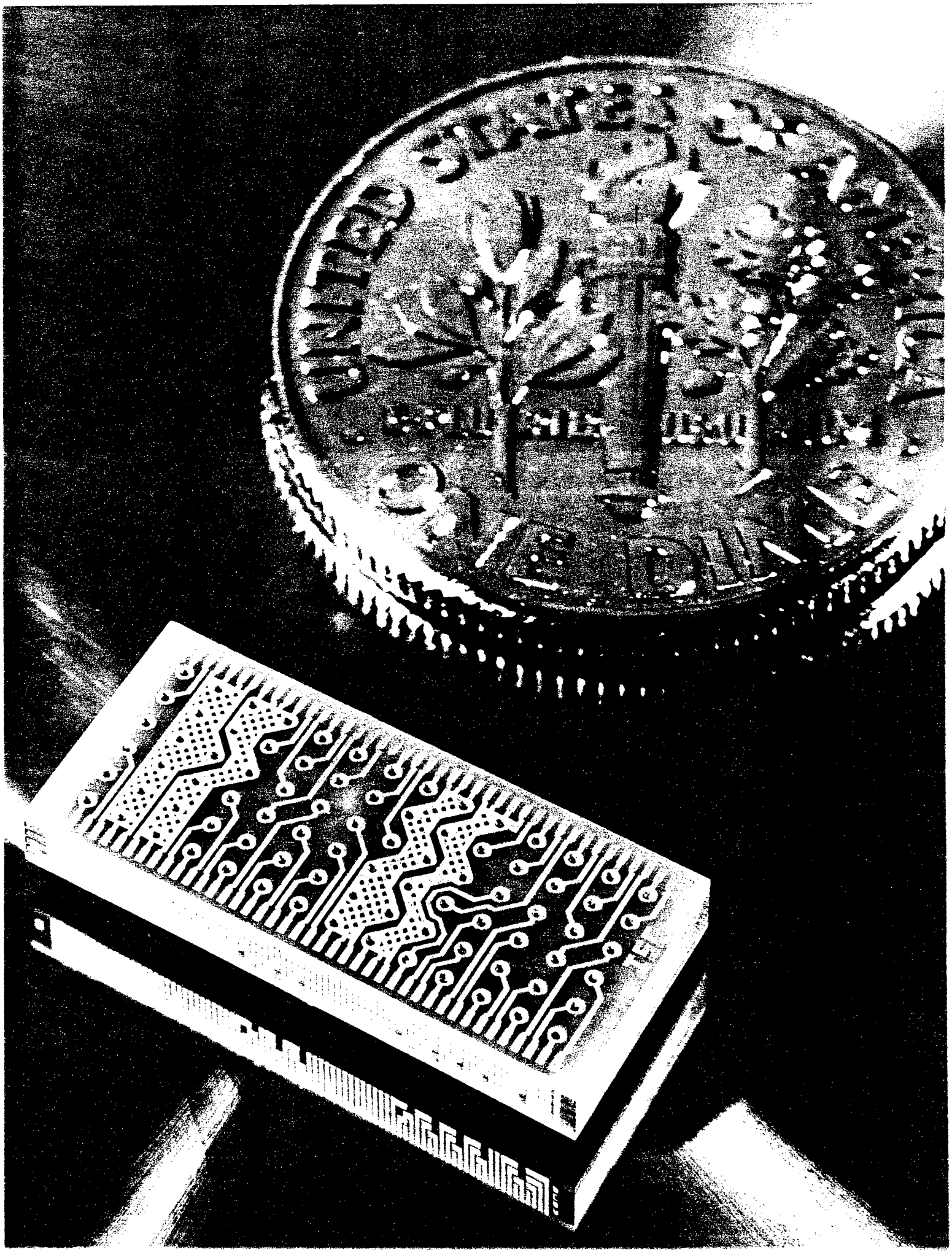


In this report we highlight advances in biomedical applications of BMDO technology.

The SBIR and STTR programs are administered by BMDO and other government agencies to support and develop cutting-edge technologies and lead them to the American marketplace. SBIR concentrates on funding proof-of-concept and prototype product development in small business settings, and STTR fosters cooperation between nonprofit research institutions and businesses. The IS&T program is designed to quickly galvanize high-risk technology through targeted research and development. In addition, IS&T seeks to shorten the interval between concept and application. The TA program promotes commercialization of advanced technologies and cross-fertilization of ideas between government agencies. Through technology review meetings with small businesses, outreach publications, and a proactive stance in disseminating information about new commercialization efforts, the TA program nurtures the seedlings of technology transfer.

With decreasing government spending and continuous pressure to reduce the national deficit, all government agencies are aware of the need to make every dollar count. BMDO has operated from its inception with an eye to dual use, and in 1994 it began to pursue a relationship with the Department of Health and Human Services to transfer BMDO-funded technologies to the area of breast cancer detection and prevention. BMDO has also joined the Federal Multi-Agency Consortium on Imaging Technologies to Improve Women's Health, a concerted government effort to develop advanced imaging technologies for improved screening, earlier diagnosis, and better treatment of breast cancer. The consortium includes representatives from the Central Intelligence Agency, the U.S. Army, the Defense Advanced Research Projects Agency, the National Aeronautics and Space and Administration, the National Cancer Institute, and the National Science Foundation, to

name just a sampling. This group is headed by the office of the Assistant Surgeon General and Deputy Assistant Secretary for Health (Women's Health). The consortium's technology transfer subcommittee put out a request to 297 Federal agencies and laboratories to submit potential technologies that could advance digital mammography, magnetic resonance imaging, ultrasound, nuclear medicine, computer-aided diagnosis, 3-D visualization, and image storage and transmission. Of 82 technology responses, the subcommittee chose 14 for funding consideration; of these, 6 were BMDO submissions. These technologies were large-format digital sensors, avalanche photodiodes, acousto-optic tunable filters, active vibration isolation systems, uncooled infrared cameras, and polarization imaging and fluorescent spectroscopy devices. BMDO continues its cooperation with the consortium through meetings and technology development.



Some regard the information revolution as the most significant event of the 20th century. Whether we are researchers, bank tellers, insurance underwriters, supermarket cashiers, or stockbrokers, we deal with sometimes overwhelming quantities of information. Those who study the education process have consistently found that how information is presented is key to retaining facts, organizing data, and consolidating important memories. Often, the combination of compelling visual display and pertinent text, whether written or spoken, is highly successful in making a long-term impression on the learner. Sometimes, visual display is the only means of effectively conveying information. It takes far more effort to outline in words the key sensory pathways in the brain, or the distinguishing features of a malignant breast tumor on a mammogram, than to simply study the images and store them as principally visual memories. Since these images do convey so much information, it seems fitting that they would require large amounts of memory for storage, and indeed they do. In addition, high-quality, high-resolution imaging requires very rapid data transfer rates.

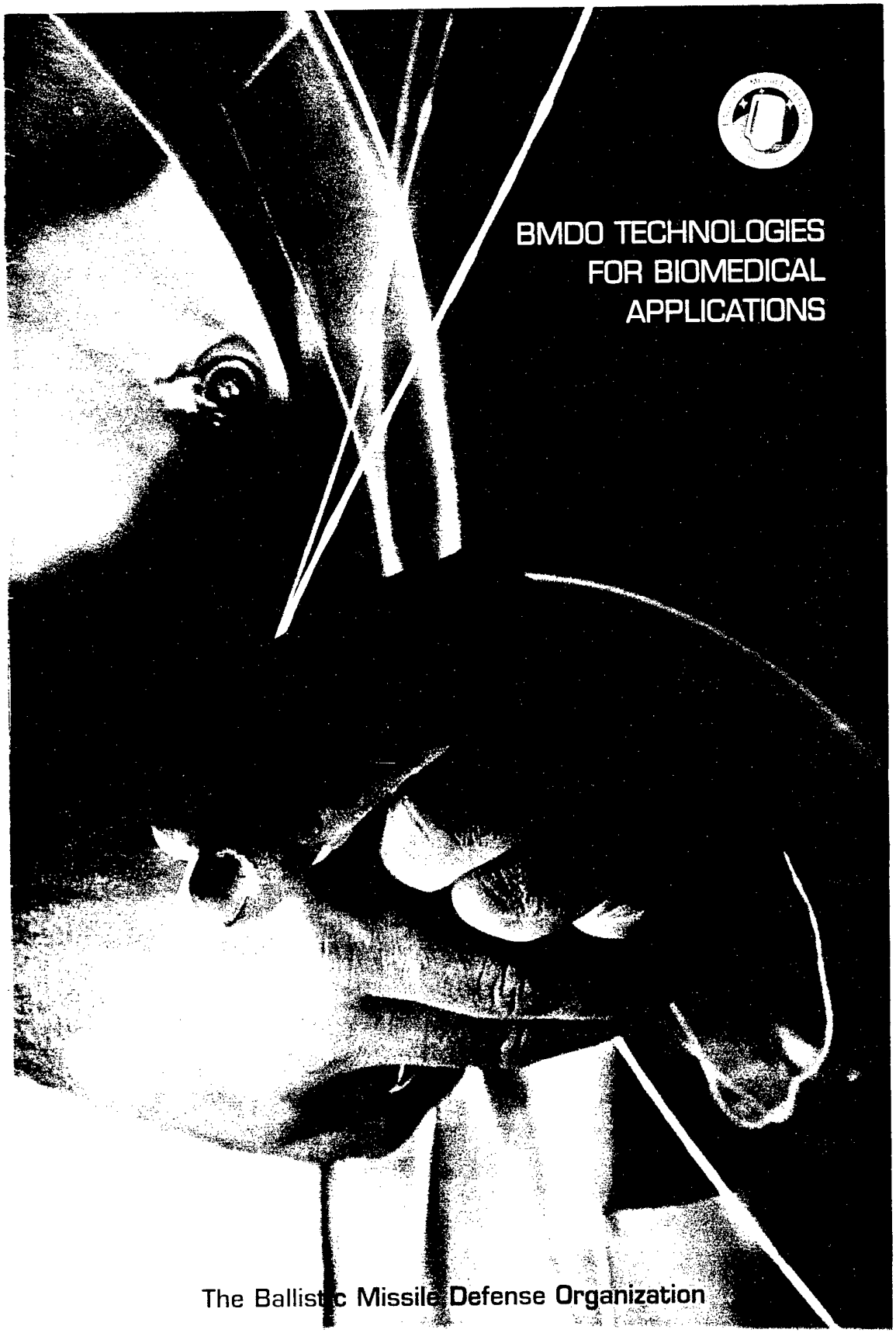
3-D Picture in a Cube

AstroTerra's 3-D Volumetric Display

Award-Winning High-Speed Optical Processor

Chip-Stacking Technology from Irvine Sensors & JPL

Fiber-Optic Testbed at UCSD Under Way



BMDO TECHNOLOGIES FOR BIOMEDICAL APPLICATIONS

The Ballistic Missile Defense Organization

ADVANCED TECHNOLOGIES FOR MEDICINE AND BIOLOGY

"There can be no greater peace dividend from our national investment in defense than to improve the health of our citizens."

Susan J. Blumenthal, M.D.

How do light and matter interact to produce the latest advance in cancer treatment, and what in the world does it have to do with the Department of Defense? How did a search for high-volume data storage result in a novel, radiation-free gene probe? How can a microchip that flies on defense satellites improve the regimen of a radiotherapy patient? All of these questions are explored in a new report from the Ballistic Missile Defense Organization, *BMDO Technologies for Biomedical Applications*.

In this report, we are highlighting BMDO-funded technologies and how they have found their way into biomedical innovations and evolutions. Focused on three main areas of interest; observation, detection, and intervention, the report covers 33 companies and institutions.

For example...

■ **3-D Technology Laboratories is developing a three-dimensional display that is truly visible from all angles, without awkward glasses...**

This display can offer models of anatomy that are not limited by the usual obscuring barriers, such as a transparent view of the human brain, seeing the skull and all the internal structures at once. It takes virtual reality beyond what is possible in actual reality to see any solid as a sort of 3-D line drawing.

■ **Mediscience Technology Corporation is using its recently approved endoscope to monitor cancer drug trials at Memorial Sloan-Kettering Cancer Center...**

A doctor specializing in cancers of the head and neck is using Mediscience's specialized CD-Scan endoscope as part of an ongoing phase II drug trial. The endoscope can examine the light signature of tissue and check, in real time, the response of the patient to the drug.

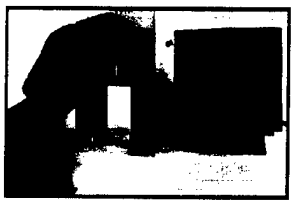
■ **PurePulse Technologies offers a cheap, rapid, effective way to kill microorganisms such as E. coli or Cryptosporidium...**

The newspapers are strident with reports of antibiotic-resistant bacteria and our nation's burgeoning problem with food-

and water-borne infections. In response to this widespread concern, PurePulse has introduced a novel "cool" technology that safely eliminates bacteria, viruses, and hard-to-kill spores.

■ **Applied Modern Technologies' eye tracker can bring expert diagnosis to remote and underserved communities...**

This adaptive optics-based technology could allow an ophthalmologist to evaluate a patient's eyes from miles away. Closer to home, the quick, accurate, and automated eye screening device is an ideal tool for producing more accurate corrective lens prescriptions.



■ **Essex Corporation has introduced a unique Virtual Lens Microscope™ that can give scientists an unstained view of living systems...**

Scientists want to view living systems in a natural state to understand the physical and chemical basis of life. Such knowledge enables us to diagnose and fight disease. This microscope, based on radar technology, can rapidly acquire a 3-D image of living matter without altering its structure.

Our new report details the latest developments in BMDO technologies that can assist the life sciences.

■ To obtain this new report, ***free of charge***, you may:

- Mail the completed form to *BMDO Technologies for Biomedical Applications*
  Ballistic Missile Defense Organization
  c/o National Technology Transfer Center,
  Washington Operations
  2121 Eisenhower Avenue, Suite 400
  Alexandria, Virginia 22314
- Call NTTC/WO at (703) 518-8800, ext 500 or
- Fax your request to (703) 518-8986 or
- E-mail the editor at joan@nttc.edu

Printed on recycled paper.

SECTION A
PRESENTATION

Those involved in ballistic missile defense need to quickly and efficiently identify objects and classify them as friend or foe, gain a "big picture" view of the ever-changing battlefield, and track missiles in three dimensions. Similarly, doctors need to distinguish between benign and malignant growths and require high-resolution images with a sufficiently large format for optimal viewing. Surgeons especially can benefit from the gradually evolving virtual-reality displays that employ 3-D imaging techniques. The military's interest in display technology has yielded some promising cutting-edge ideas for displays in general, with applications in many areas, including medicine.

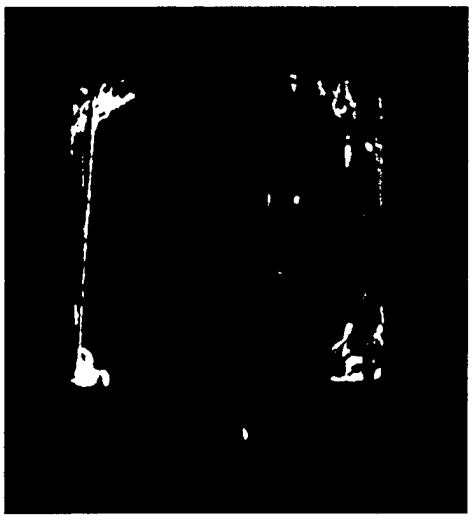
1. A novel 3-D display that uses a rare-earth-doped glass cube to create a truly three-dimensional, hologram-like image that can be viewed from any angle.

2. A prototype 3-D display that intersects two laser beams in rubidium vapor, generating visible red fluorescence, with promise for full-color applications.

3. A high-speed optical processor that resulted from BMDO work on an incoherent-to-coherent converter for optical computing.

4. A chip architecture that stacks integrated circuits and interconnects them vertically, translating to faster data processing and downloading.

3-D PICTURE IN A CUBE



This prototype display offers true 3-D without illusions.

Some neuroscientists theorize that we store information in our brains holographically, with each memory stored in several places simultaneously. When we remember something, all these areas are alerted at the same time from one prompting neuronal signal, much as a laser can tease out an entire image from a hologram with one beam. Perhaps this is why we relish 3-D reconstructions.

BMDO HISTORY

3-D Technology Laboratories (Mountain View, CA) was founded by Elizabeth Downing, Ph.D., in 1996. Her pioneering work in 3-D display technology at Stanford University generated enormous interest and earned widespread publicity. Along with a number of agencies, BMDO is helping to support her research in rare-earth-doped glass display technology through a Phase I SBIR contract. The applications are numerous, ranging from medical imaging and air traffic control displays and battlefield management monitors to video games and virtual-reality entertainment devices.

HOW IT WORKS

The system uses two computer-controlled infrared lasers to trace its 3-D pictures inside a cube of special laminated glass, much as the electron beam from a cathode ray tube traces a 2-D image on a television screen. The energy generated at the point where the invisible laser beams intersect makes a single point of the glass glow with visible light—a precise dot like a video screen pixel seemingly suspended in space. "This allows you to address a pixel anywhere inside a three-dimensional volume, and then by scanning rapidly, you can draw three-dimensional images," says Downing. The fluorescent glass display uses several rare-earth compounds that emit different colors of visible light when struck by the laser beam. By varying the chemistry of the glass, the designers are able to generate red, blue, and green light and mix them to create all the components necessary for a full-color display.

The prototype display is about a cubic inch in volume, and the pictures it contains are simple three-color line drawings, which serve as test patterns. But its developers said they are confident that they can quickly make the viewing system larger while making its support electronics smaller. Standing between the developers and any immediate commercial application are technical obstacles such as the cost of the high-purity materials needed to manufacture the special rare-earth

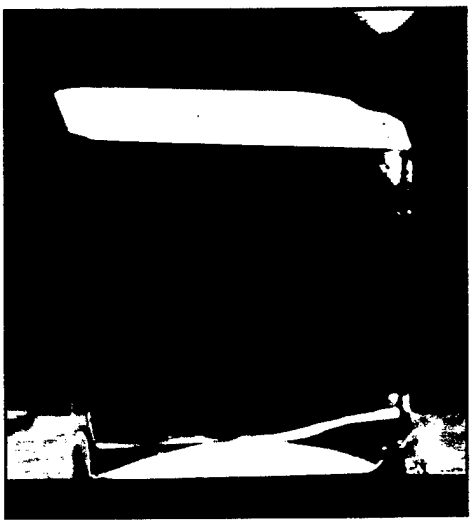
glass used in the display cube. In addition, the processing demands imposed by data-intensive, high-resolution imaging are quite high.

MEDICAL SIGNIFICANCE

The display draws real volumetric images. As a result, all the normal depth cues that are used for visualization can be applied, independent of the user's head position. No processing has to be done to update the view when the user's perspective changes. This is one of the primary differences between true 3-D and virtual-reality or stereoscopic displays—no latency due to rendering scenes from a new direction. The unique advantages of this system lend themselves exceptionally well to medical imaging.

The display can offer models of anatomy that are not limited by the usual obscuring barriers. As an example, a surgeon could observe a transparent view of the human brain, seeing the skull and all the internal structures at once, as if they were made of glass. This is an interesting way to look at physical models. It takes virtual reality beyond what is possible in actual reality—to see any solid as a sort of 3-D line drawing. By referring to landmarks in the display, surgeons can be more confident that they are avoiding vital arteries and other areas as they move their instruments. A different view can be obtained by simply looking at a different part of the display.

As a teaching tool, current 3-D displays are already immensely popular. Animation and viewability from any angle are further advantages of the new technology. The heart in motion, for instance, is a far more informative representation than a static model.



● *Designs can range from whimsically simple to complex.*

VENTURES OR PRODUCT AVAILABILITY

This technology is in the research phase. Downing has obtained generous support from the National Science Foundation, the Air Force, the Defense Advanced Research Projects Agency, and the National Aeronautics and Space Administration, and is submitting a Phase I SBIR proposal to the National Institutes of Health. She has recently made a technical advance by incorporating praseodymium into a ceramic glass, which could reduce the cost of materials.

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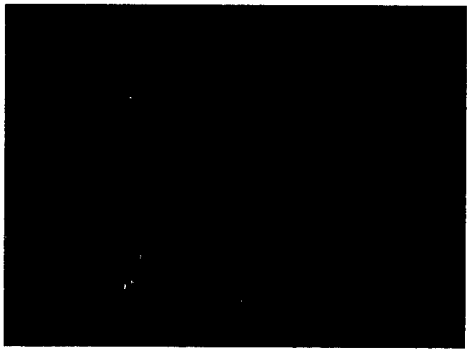
ASTROTERRA'S 3-D VOLUMETRIC DISPLAY



● *This early-stage display requires no special glasses for viewing.*

The World Wide Web is a host to many medical image sites, some of which are incorporating 3-D imagery to increase visual interest and interactivity. Now if only the information pipeline could widen enough to accommodate all these images!

BMDO HISTORY

AstroTerra (San Diego, CA) demonstrated a 3-D display during a BMDO Phase I SBIR contract and is looking for a commercial partner to help define the direction of a Phase II development effort. BMDO is intrinsically interested in 3-D representations of objects in space and in the atmosphere. Tracking airborne objects is a job best done in three dimensions, as each object has three coordinates. A task such as air traffic control derives its stressful nature, in part, from continually translating 2-D data into meaningful 3-D positions.

HOW IT WORKS

The display technique intersects 630- and 780-nanometer laser beams in rubidium vapor, resulting in a visible red fluorescent image at the intersection point. Quickly scanning the intersection point in a given pattern creates a 3-D image that can be viewed from any angle. By adding lasers of different wavelengths, it is also possible to create green and blue fluorescence patterns and eventually produce a full-color display. AstroTerra licensed the patent on this technology from ThermoTrex Corporation (San Diego, CA) based on work done at ThermoTrex by AstroTerra's current president.

MEDICAL SIGNIFICANCE

In procedures such as brain surgery, anatomy must be understood and mapped as precisely as possible. Surgeons rely on computerized axial tomography scans, conventional x-rays, and magnetic resonance imaging studies to build a piecemeal 3-D picture to determine relative positions of problem areas. Increasingly sophisticated image-processing techniques are helping to fuse information from these diverse imaging modalities to create a realistic model of human organs. Since the surgeon will be operating in a three-dimensional space, a 3-D image better represents surgical landmarks and helps bring precision to the operating theater. An image that can be seen from any angle adds more realism to the scene.

For medical training, 3-D imagery is also invaluable. First-year medical students spend much of their time dissecting cadavers to learn anatomy and physiology. While virtual-reality models of the human body probably will not replace cadavers entirely, 3-D imagery and interactive manipula-

tion can certainly add to medical education. A far more likely and widespread use of this application would be in general biology. Students in secondary schools and universities are turning away from performing traditional frog and rat dissections, frequently on ethical grounds, in favor of studying virtual animal models.

VENTURES OR PRODUCT AVAILABILITY

Thus far, the technology has produced simple monochromatic (red) images of cubes and a rotating globe.

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AWARD-WINNING HIGH-SPEED OPTICAL PROCESSOR

Apoptosis, or cell suicide, is thought to play a role in AIDS, autoimmune diseases such as lupus, and cancer. The p53 tumor suppressor, mutations of which are found in about half of all cancers, is a gene that controls the pathway to cell death.

This optical processor can sharpen all types of medical displays.

BMDO HISTORY

Silicon Mountain Design, Inc. (SMD; Colorado Springs, CO), has designed an optical processor that can be used with visible and infrared light, as well as for x-ray applications. This technology grew from a BMDO SBIR Phase I project to develop an ultrahigh-speed incoherent-to-coherent converter for optical computing, meant for automatic weapons targeting. The converter and processor have applications in night vision and image compression.

HOW IT WORKS

SMD used a combination of micromachining technology and ultrathin-wafer processing to put a charge-coupled device (CCD) and a spatial light modulator (SLM) on the same chip. Because the SLM directs light onto the CCD, the light conversion is described as "incoherent to coherent." This parallel arrangement eliminates the data bottleneck at the processor input, so images can be acquired much more rapidly than with a serial input arrangement. The result is a high-speed camera that has medical and industrial applications. As an example, the SMD Mach-I digital camera can run at 1,000 frames per second with spatial resolutions from 256 x 256 to 512 x 512 for 8-bit pixel depths. The camera's parallel optical input features help to eliminate image smearing common to other high-speed cameras.

MEDICAL SIGNIFICANCE

The high-speed processor can improve the image quality in x-rays, mammograms, and visible-light micrographs. High-speed image processing is crucial for quickly downloading high-resolution medical images, screening micrographs such as those used in automated diagnostic systems, and capturing rapidly occurring events in living cells. For real-time fluoroscopic imaging, in which x-rays are used to image cardiac catheterization and angiography, the optical processor could improve image clarity. The imager could also to be used in tandem with recently approved computer-aided diagnostic systems for Pap smears. Another application is in evaluating calcium ratios in cell samples to determine rates of cell death. Calcium release

can signal cell membrane rupture and subsequent cellular demise. Apoptosis, or programmed cell death, is an emerging field that continues to increase our understanding of the mechanisms behind cancer development and aging.

VENTURES OR PRODUCT AVAILABILITY

SMD is currently performing demonstrations and negotiating with two large medical imaging companies and two major automotive manufacturers. The company continues to investigate applications in industrial areas such as product inspection on assembly lines, and particulate matter in lubricants and hydraulic fluids.

SMD is also working with the University of Colorado at Colorado Springs to develop a solid-state miniaturized imager with a disposable imaging head for use in endoscopic procedures.

SMD received the SBIR Technology of the Year Award for its optical processor at the October 1995 Technology 2005 conference, held in Chicago. The next year, SMD won the Grand Award for its SMD-1M60 camera at the October 1996 Technology 2006 conference, also held in Chicago.

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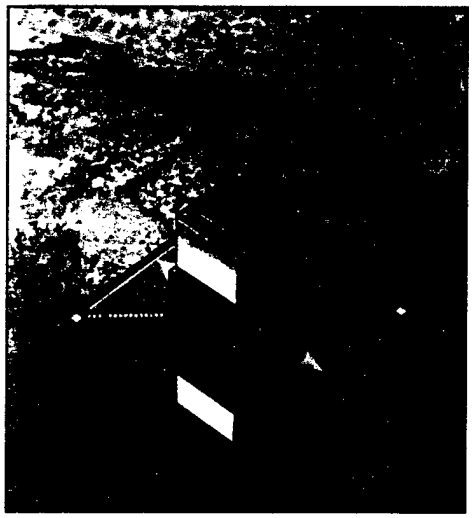
CHIP-STACKING TECHNOLOGY FROM IRVINE SENSORS & JPL



3-D neural networks can quickly process and analyze images.

Visual processing takes up a little more than half the brain's workload. Humans are so pictorially oriented that the blind can interpret touch as a visual signal. Neural activity in areas of the brain that subserve vision can be stimulated by tracing outlines of simple objects on the skin of a blind subject.

BMDO HISTORY

To fit ever more circuitry into computers, manufacturers and designers have demanded narrow line widths and novel chip architectures. Chip stacking is one approach to both increase the speed and decrease the size of multichip modules (MCMs). This 3-D architecture would shorten chip interconnections, thus producing smaller, faster MCMs. BMDO has funded research into this technology at Irvine Sensors Corporation (ISC; Costa Mesa, CA) and the Jet Propulsion Laboratory (JPL; Pasadena, CA) for a number of programs, including VIGILANTE, an Innovative Science and Technology project that has as its goal the development of a neural-network module that can perform image recognition.

HOW IT WORKS

ISC creates its MCMs by thinning each wafer layer to less than 100 micrometers, patterning it, and dicing it to form separate integrated circuits. After surface metallization, the chips are stacked together, aligned, and bonded with a thermally compatible epoxy. Raised metallic leads on the surface of each chip provide electrical contact between adjacent chip elements. These through-thickness electrical connections reduce circuit path lengths and thereby increase the module's operating speed. The shorter current paths also reduce overall power consumption.

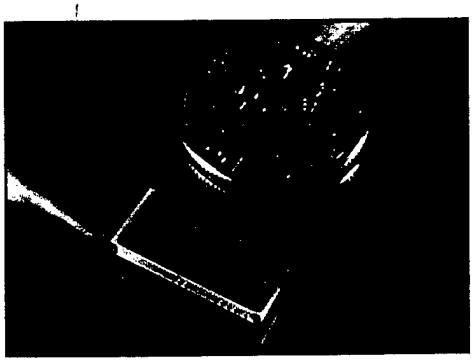
Using this technology, ISC and JPL are working on a 3-D neural-network microprocessor. Artificial neural networks are designed to behave approximately as human brains are thought to function; they enable pattern recognition and learning behaviors that are difficult for conventional computers to handle. Thus, a neural-network processor involves large numbers of data and processing nodes that continuously interact with each other. The ISC chip-stacking techniques can achieve the high interconnection densities necessary to construct an efficient and fast neural network.

JPL and ISC jointly developed and designed a 3-D neural-network microprocessing module called 3DANN™, as well as a new device called the Neural Processing Module (NPM). The 3DANN module is three-quarters the size of two stacked sugar cubes; 64 of them will be integrated into a cube to form the NPM. Mounted on the cube will be a column loading

input circuit chip to convert video data from digital to analog form for parallel processing. This image-processing device is expected to be able to perform specialized functions at up to a trillion operations per second.

MEDICAL SIGNIFICANCE

Medical imaging applications demand an enormous amount of data throughput for downloading and reviewing x-rays, computed tomography scans, MRIs, and ultrasound studies in a timely and clinically practical manner. Just one mammogram can contain 24 to 40 megabytes of pixel data. Considering that a single radiological consult on a suspicious mammogram requires eight separate images (four current views compared with four historical views), one patient means 192 to 320 megabytes of data. Anyone who has twiddled thumbs while downloading mere kilobytes of data over a pretty good T1 line will immediately recognize the problem. ISC's device can process more than 15,000 images that are 64 x 64 pixels each, while the embedded neural network can supplement the throughput function with computer-aided diagnosis software. As filmless or digital mammography comes into common use, the 3-D processor will be inherently compatible with such systems.



This compact processor will meet the needs of shrinking device sizes.

VENTURES OR PRODUCT AVAILABILITY

A military demonstration of the chip is scheduled for late summer 1997.

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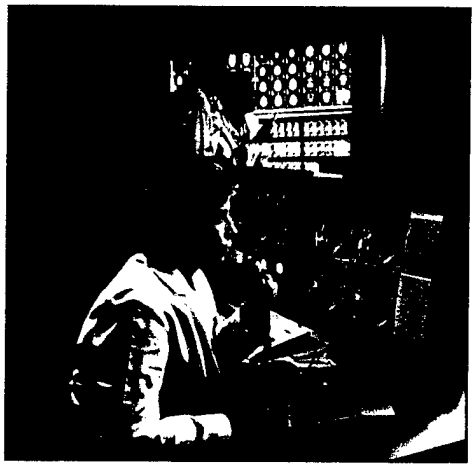
SECTION B
STORAGE AND TRANSMISSION

While remarkably compact in conveying meaning to our brains, visual information takes up a lot of space in electronic form. And as many have discovered to their foot-tapping chagrin, it also takes an awfully long time to download. War-weary military planners and HMO-frazzled doctors alike must be able to store and quickly recall information if it is to be of value. A wider data-transfer conduit can be achieved in a number of ways; fiber-optic technologies have already greatly improved and continue to increase the carrying capacity of the information pipeline. In addition, new optical media can be manipulated to store data more compactly.

1. A university-based network testbed that will employ advanced optical switching and multiplexer technologies to enable distributed image processing and shared access at transfer rates greater than 1 gigabit per second.

FIBER-OPTIC TESTBED AT UCSD UNDER WAY



High-speed networks help doctors see important information quickly.

Fiber-optic systems will be crucial to implement President Clinton's call to connect the nation's schools, libraries, hospitals, and clinics to the National Information Infrastructure, better known as the Internet, by the year 2000.

BMDO HISTORY

The University of California at San Diego (UCSD; San Diego, CA) is developing a regional network devoted to medical imaging as part of a consortium on photonic computing networks. This effort is being funded by BMDO through a Focused Research Initiative on Photonics for Data Fusion Networks. The network will employ advanced optical switching and multiplexer technologies to enable distributed image processing and shared access at gigabit-per-second transfer rates. Defense agencies in general are interested in similar high-speed networks that can link real-time surveillance, simulations, and archived geographic data for battle management. Confidentiality and security during information transfer are also major concerns for medical practitioners and hospital administrators.

HOW IT WORKS

The testbed network links several UCSD medical departments, the School of Medicine, a computer engineering department, a regional Veteran's Administration Medical Center, NASA's Jet Propulsion Laboratory, and the San Diego Supercomputer Center. The UCSD effort to date has concentrated on determining the imaging volume for computed tomography (CT), magnetic resonance imaging (MRI), ultrasound, and x-ray diagnostic needs, from the standpoint of storage and retrieval requirements as well as traffic management on the network. The researchers have also undertaken an extensive study of clinical needs, to include both the quality and presentation of the image data and the real service needs of the user. Real needs would include how fast a physician can pull up a patient history or a clinical image, access to monitors in the radiology department, large enough screens for comparative studies (such as comparing past mammograms with present ones), search engines for finding records, and even allowance for the radiologist's traditional reliance on grease pencils and film images.

MEDICAL SIGNIFICANCE

Information management and image presentation have become an area of concentration for clinicians and administrators alike. Systems must be user friendly, quick to respond, and above all accurate. So far, the UCSD project has yielded a prototype system at the UCSD Hillcrest Center that allows radiologists to use a touch screen to manipulate images and patient

records on eight high-resolution monitors. All monitors are dual purpose, displaying either images or text. Doctors can view eight full-size x-ray images at once. Smaller systems have been developed for an intensive care unit, allowing for seamless interaction between patient databases and the physician. Currently, data transmission with a small sample database is performed over an Ethernet connection at 100 megabits per second.

In addition, the project is also planning a line-of-sight laser linkage between Hillcrest Center in San Diego and another participating center in La Jolla.

VENTURES OR PRODUCT AVAILABILITY

The technical objectives of the UCSD program are to explore and eventually implement a scalable third-generation terabit-per-second photonic network architecture and protocol for distributed imaging environments. In addition, the project will investigate spectral-domain processing using ultrashort pulses for terabit-per-second data rates and will address security issues using classical and quantum cryptography. UCSD will also develop network interfaces between fiber-optic imaging networks and wireless networks. There is a considerable R&D phase ahead before the photonic testbed is actually constructed. Conventional connections (such as the Ethernet mentioned above and ATM) are now being used to develop the practical framework of this initiative.

Data fusion in real time, such as superimposing MRI images over CT images, is another goal of this project. Work in this area is being performed at Brown University (Providence, RI).

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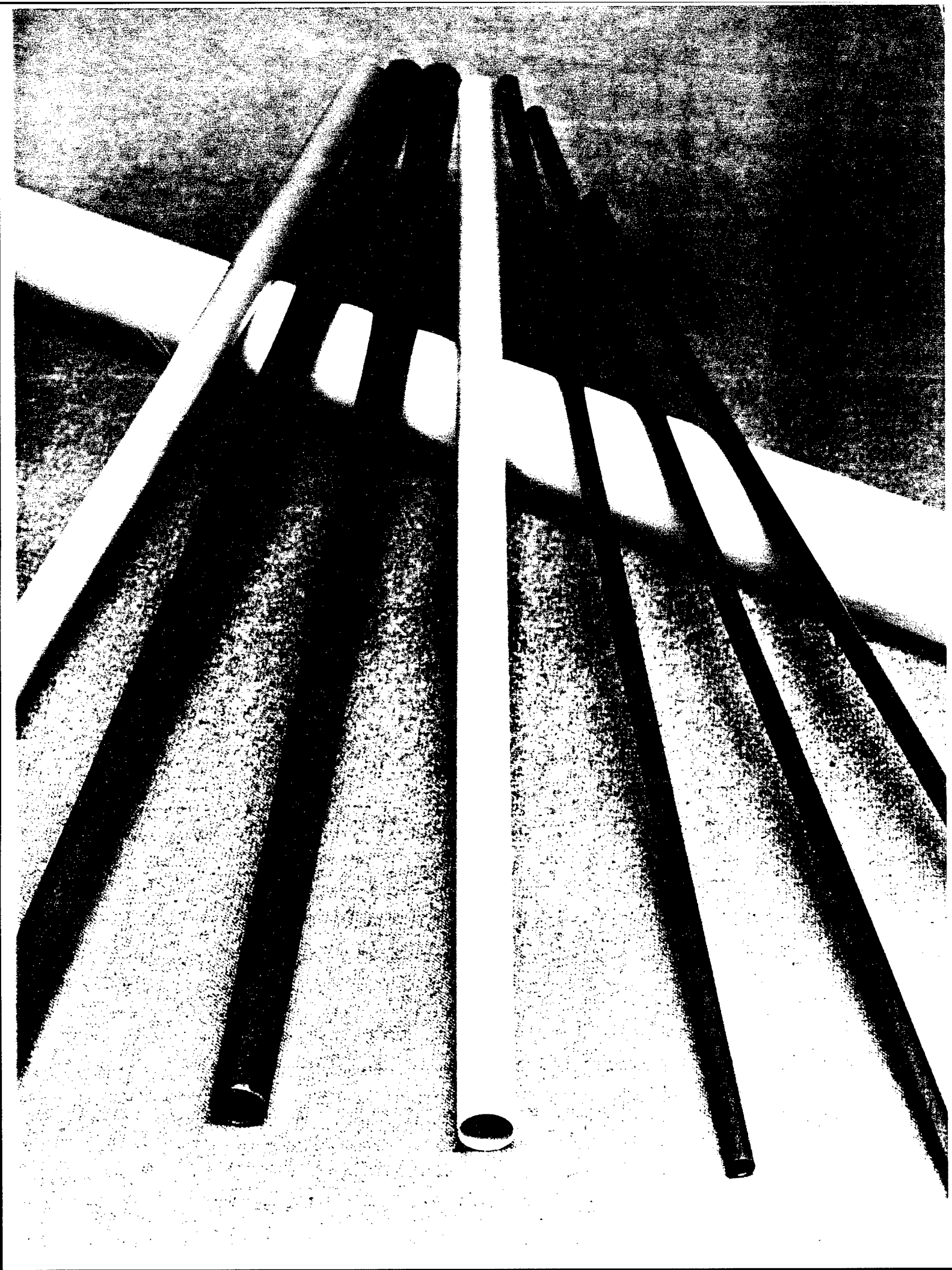


Biomedical researchers rely on many different methods to help them see beyond the facade that hides the workings of the organism. We have seen a revolution in our ability to decipher the processes that control growth and metabolism, and the diseases that result when these processes are disordered. The methods used are diverse and represent intersections between disciplines that have long operated on parallel tracks. Now the physics that produced lasers and radar meets the biology that brought us awareness of the molecules of life. Materials science crosses paths with medical interventions such as laparoscopy and implant surgery and with biotechnology tasks such as genetic analysis. Spectroscopy, once the domain of chemists and astronomers, now helps to identify plaque in the lumen of arteries and even the presence of cancer.

Essex Corporation's Virtual Lens Microscope™
Simple Isotope Separation
Superex Polymer Tubing
Chip-Sized Radiation Monitor

Versatile Tunable Filter for Optical Tasks
High-Speed Molecular Modeling
LiSAF Laser for Cytometers

AMT: Binocular 3-D Eye Tracker
Deformable Mirrors to Uncover Eye Disorders
NIH Infrared Microscope
Advanced Imaging Spectrometer
MTC's Endoscope
Raman-Based Gene Probe Technology
Nanophosphors
Optical Biopsy
Sagebrush Gimbal for Needle Biopsy

SECTION A
DETECTION

Nondestructive testing allows us to study life with minimal alteration and disruption. Minimally invasive methods to diagnose disease are increasingly relied upon to reduce risk and discomfort to the patient. We monitor our surroundings to detect harmful environmental influences and prevent their deleterious effects. Radioactive tracers can pinpoint tumors, detect stroke damage, and assist in metabolic studies. All these important enterprises have benefited from evolution and innovation in technology.

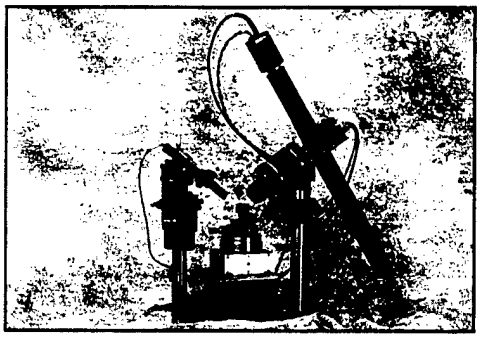
1. A synthetic aperture radar microscope that can produce high-resolution 3-D images within seconds.

2. An isotope separation method that economically produces carbon-13 for diagnostic tests.

3. A high-strength, sterilizable polymer tubing that is both versatile and economical.

4. A low-cost, compact radiation monitor that can better quantify radiotherapy regimes as well as protect workers in nuclear medicine.

ESSEX CORPORATION'S VIRTUAL LENS MICROSCOPE™



● *This microscope will support new standards in nondestructive analysis.*

Antony van Leeuwenhoek first observed "animalcules" in the 17th century with a magnifying lens, not the compound microscope of his British contemporary, Robert Hooke. However, Leeuwenhoek's lens-grinding skill and acute eyesight allowed him better resolution with his one-lens system than with the inferior two-lens system of the period.

BMDO HISTORY

Essex Corporation (Columbia, MD) has developed a Virtual Lens Microscope™ (VLM), based on the principles of synthetic aperture radar (SAR), that can produce high-resolution 3-D images in a few seconds. The microscope uses coherent light, in tandem with Essex's patented ImSyn image processor, to produce holographic images with a resolution of one-quarter the incident wavelength used to illuminate the object. BMDO sponsored the development of a wideband range-Doppler imager for ground-based radar, from which both ImSyn and the VLM resulted.

HOW IT WORKS

The VLM can operate in the ultraviolet, visible, infrared, and microwave regions of the spectrum. Thus if the operating wavelength is in the ultraviolet sector, objects as small as 70 nanometers, or one-hundredth the diameter of a human hair, can be resolved. The VLM's resolution is also independent of working distance, so very small images can be resolved from several inches away. The ImSyn optoelectronic processor uses a two-dimensional, discrete Fourier transform algorithm to produce a 256 x 256 pixel, 32-bit complex-valued transform (equivalent to 65,536 samples processed) in as little as 50 milliseconds. Conventional methods such as data regridding followed by a fast Fourier transform image reconstruction are not rapid enough to provide the high throughput and rapid data processing needed for a variety of imaging modalities, including VLM, spiral magnetic resonance imaging, and computed tomography.

MEDICAL SIGNIFICANCE

A nondestructive microscope that can image features as small as 70 nanometers would be ideal for viewing cell organelles, chromosomes, and organic molecules. Unlike electron microscopes, which require considerable alteration of the sample, or two-photon confocal microscopes, which have problems with photobleaching (image washout), the VLM can provide a three-dimensional view of living matter with minimal preparation. Researchers in molecular genetics, cellular and molecular biology, all

aspects of medicine, and physiology would find the VLM a diverse tool for gathering accurate information about life processes.

VENTURES OR PRODUCT AVAILABILITY

Essex has a working relationship with the University of Maryland Medical School for the study of video-rate MRI images produced by the ImSyn processor and is also targeting the defense market for applications of ImSyn and SAR technologies, including VLM. The first SAR processor was delivered in late 1996, with several orders placed for delivery in the first quarter of 1997. SAR can penetrate foliage, camouflage, and shallow soil to detect vehicles, buildings, mines, and other objects that cannot be detected by conventional radar systems.

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SIMPLE ISOTOPE SEPARATION

● *A faster, cheaper method of separating isotopes can help visualize brain function.*

For decades, gastric ulcers were considered a result of excessive stomach acid production or stress, until a determined researcher deliberately drank a solution containing *Helicobacter pylori*. It took just a few more years to confirm that the bacterium causes the great majority of ulcers in the stomach.

BMDO HISTORY

NanoDynamics, Inc. (New York, NY), developed a method for separating carbon isotopes through a BMDO Phase I SBIR contract for synthetic diamond film growth. BMDO has had a long-term interest in diamond substrates because of their superior thermal and conductive properties in microelectronic devices. Through this research, NanoDynamics found an economical method of separating carbon-12 and carbon-13 from natural carbon sources. The method can reduce the cost of enriched carbon-12 from $100 to less than $10 per gram.

HOW IT WORKS

NanoDynamics' separation process takes advantage of the difference between the masses of the two isotopes, in a method called time-of-flight separation. The methane gas from which the carbon isotopes are isolated is accelerated to supersonic speeds, and the two isotopes are collected from two separate rotating nozzles. This "garden hose" separation method is much more cost-effective than conventional distillation methods.

MEDICAL SIGNIFICANCE

Carbon-13 is a nonradioactive isotope that has at least two medical applications in diagnostic medicine. The first is as a constituent of urea, which is administered orally as part of a simple test for the ulcer-causing pathogen *Helicobacter pylori*. The bacterium ingests the urea and excretes it as carbon dioxide (CO_2) as part of its metabolic waste. With a breath analyzer, the expired CO_2 is analyzed for isotopic content, indicating the presence or absence of the bacterium. The breath test is a major improvement over the two alternative procedures for detection, blood tests for antibodies to the organism and endoscopic stomach biopsy.

A similar breath test can be used for nutritional studies, but with amino acids tagged with the isotope. This information can be used to study rates of protein turnover (how fast one uses proteins), energy expenditure (metabolic rate), and nutritional availability of certain foodstuffs.

Because it has properties that make it easy to detect in an MRI examination, carbon-13 can also be used as a constituent of glucose for functional MRI studies. For instance, glucose utilization in the brain is routinely studied as a window into brain function. Neurologists ask patients to perform tasks and observe which areas of the brain "light up" because of increased glucose utilization. In this way, researchers can deduce the basic functions of brain areas, and clinicians can assess patients for loss or gain of function during the course of a disease.

VENTURES OR PRODUCT AVAILABILITY

NanoDynamics is seeking partnerships to develop products.

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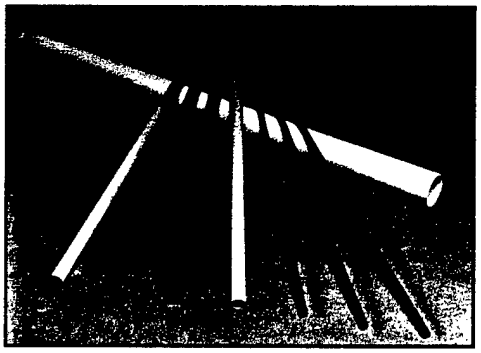
SUPEREX POLYMER TUBING



● *Reusable and rugged tubing for endoscopic procedures—an unexpected result of defense research.*

"Keyhole" surgery has recently made kidney donation a less painful experience. Instead of the wide incision formerly used to remove the donor kidney, the operation can now take place with four small punctures for instruments and a small incision for extrusion of the kidney. The new method has greatly reduced donor recovery time, blood loss, and scarring.

BMDO HISTORY

Superex Polymer, Inc. (Waltham, MA), a subsidiary of Foster-Miller, Inc., has adapted an ordered polymer technology developed originally for Air Force and BMDO cryogenic containers. In the quest for an inherently strong plastic with militarily interesting features such as radiation hardness, the company found other applications for the material. Superex uses an extrusion process that yields polymer tubing with many characteristics useful for medical, electronic, and structural applications.

HOW IT WORKS

Ordered polymers are a subset of plastics that form a self-reinforcing microstructure of fine fibers. These polymer fibers are 100 to 1,000 times finer than those used in continuous fiber reinforcement and 100 times less permeable to oxygen and water vapor than commonly used polymers. Used as a packaging material, they can provide as much protection with a single layer as other polymers provide with multiple layers. They are microwavable, sterilizable under standard autoclave conditions, and recyclable. When they are extruded as tubing, their properties of low thermal expansion, resistance to cracking, low electrical and thermal conductivity, and high tensile strength make them very desirable components for medical use.

MEDICAL SIGNIFICANCE

Endoscopic examinations and surgeries, catheterization procedures, and the new "keyhole" surgical techniques require strong, reliable fibers that can be sterilized or cheaply disposed of. In addition, some procedures have unique problems that can be addressed by small changes in the basic materials. In cystoscopy, for example, a fiber optic is placed inside a tube that is then inserted through the urethra into the bladder. A urologist can also insert the tubing beyond the bladder and into the ureters that lead to the kidneys, but the tube must be properly guided, both to avoid injury to the patient and to shorten the time spent in this semi-invasive examination. Because catheters tend to flop over once they have entered the bladder, they are difficult to control. The improved strength and stiffness of ordered polymers can make catheters easier to guide.

VENTURES OR PRODUCT AVAILABILITY

Foster-Miller has received eight patents for its ordered polymer technology. ACT Medical, Inc., is one of three companies that have licensed processing technology from Superex; at least three other companies are negotiating licenses.

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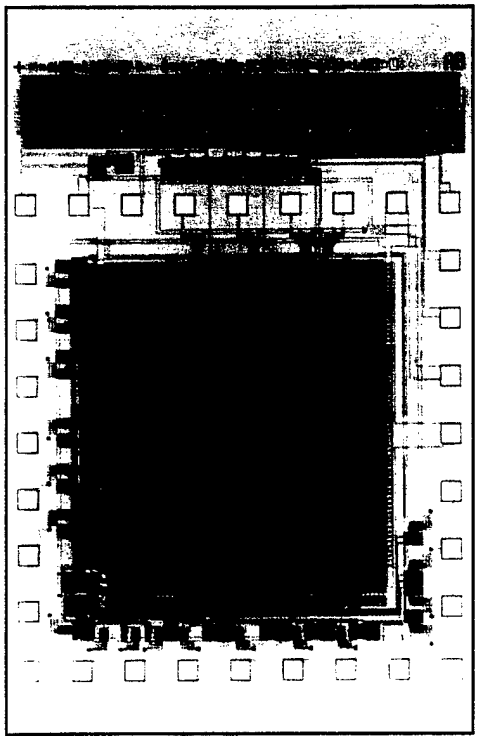
CHIP-SIZED RADIATION MONITOR



● *This multi-faceted chip can fly space missions and protect earthbound workers.*

Ionizing radiation was once considered a salubrious force. In the early part of this century, radon was sold in special inhalers as a tonic. Now, millions of dollars are spent annually to pump radon gas out of dwellings.

BMDO HISTORY

The Jet Propulsion Laboratory (JPL; Pasadena, CA) has developed a BMDO-funded, chip-sized radiation monitor that combines a total dose monitor, a particle spectrometer, and readout electronics on a single integrated circuit package. Advantages of this scheme include small size (the chip area is 1 square centimeter), low cost, and low power consumption. The monitor flew on the Clementine and Space Technology Research Vehicle (STRV-1b) space missions. In these space flights, the chip provided total radiation data from the Earth's radiation belt and tracked the radiation from a solar flare that occurred on February 21, 1994. BMDO is also sponsoring chip development for the STRV-2, in which 14 total dose monitors will fly on the Space Active Modular Materials Experiment.

HOW IT WORKS

The total dose monitor in this chip consists of two p-type field-effect transistors (p-FETs). The p-FETs operate by monitoring shifts in the threshold voltage (the gate voltage at which the chip turns from off to on) that occur when exposed to radiation.

The particle spectrometer consists of a 4-kilobit static random-access memory (SRAM) chip that is designed to enhance the "single-event-upset effect," a radiation-induced disruption of SRAMs used as memory devices. Space satellite components can be knocked out by events such as these, leading to failure of costly experiments and disruption of military and commercial satellite functions. By enhancing this effect, the SRAM can detect exposure to protons, alpha radiation, and high-energy ions. In a test aboard the Clementine spacecraft, the SRAM particle spectrometer displayed a very wide detection range, showed that it is not affected by electronics, and detected a series of solar microflares over a span of 26.5 days.

MEDICAL SIGNIFICANCE

JPL's chip has been used to calibrate proton beam delivery at the Loma Linda Proton Therapy Facility. Proton beams penetrate deeper into tissues than the x-rays used in conventional radiotherapy. For deep-seated tumors that are inoperable, proton radiation can better target the lesion without exposing the normal tissue in the path of the beam to excessive radiation. X-rays tend to deliver most of their energy at the surface, and thereafter

dissipate their energy diffusely through tissue. JPL's results show that the p-FET calibration was better than the standard ion chamber calibration, and the p-FET chip was more convenient to use. The p-FET monitors could be used during radiation treatments to ensure that neither too much nor too little radiation exposure occurred so that treatment could be safer and more efficient.

For laboratory and industry workers, this chip could also be used as a monitor for those who frequently work around radiation, including technicians in hospitals, veterinary clinics, and life science and physical science laboratories. It could be worn by power plant operators and nuclear waste cleanup crews, as well as used to separately monitor any escaping radiation. The solid-state monitors could also be checked daily, rather than monthly or quarterly, like the film badges used now.

VENTURES OR PRODUCT AVAILABILITY

JPL is developing two commercial applications for Lockheed Martin—one uses the chip as a spacecraft charge monitor, and the other will fly on the Intelsat communication satellite. JPL is also seeking commercial partners for development of radiation dosimeters for personnel, as well as for radiotherapy calibration.

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SECTION B
ANALYSIS

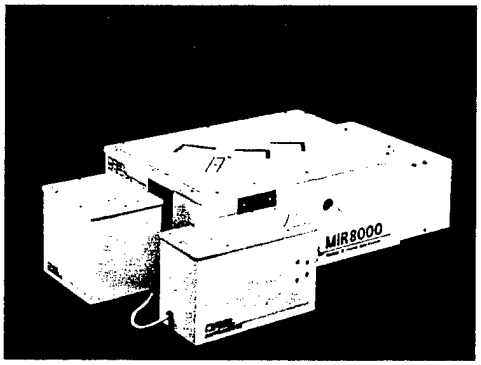
Spectroscopic methods are unlocking the chemical secrets of heart disease and cancer, enabling doctors to make diagnoses at an earlier stage of disease. Advanced computer algorithms predict critical structures that pave the way for life-saving pharmaceuticals and new antibiotics. Solid-state laser diodes light up the surfaces of lymphocytes and the interiors of nuclei, advancing research in innumerable directions.

1. An acousto-optic tunable filter that aids in the spectroscopic examination of unstable plaque in cardiac arteries.

2. A computer algorithm that increases computational speed for predicting molecular structures useful to pharmaceutical and other industries.

3. Compact, solid-state laser diodes for cytometry (cell sorting and identification).

VERSATILE TUNABLE FILTER FOR OPTICAL TASKS



● *Radiofrequency-based technology from Ciencia helped improve a common biotech task.*

Mucosal dysplasia is a precancerous condition that occurs in the gastrointestinal tract, mouth, pharynx, bladder, cervix, and lung. Cancers that originate in these areas account for a quarter million deaths per year in the United States.

BMDO HISTORY

Ciencia, Inc. (East Hartford, CT), developed acousto-optic tunable filters (AOTFs) for use in target identification and surveillance systems. In 1992, Ciencia was awarded a BMDO SBIR Phase I contract to develop a dynamically adjustable amorphous-material-based AOTF to replace birefringent crystals. Phase II funding was later awarded to pursue further development of the polymer AOTF for use in sensors. The AOTF, originally meant to capture ultraviolet radiation, has proven to be a versatile tool with a considerable impact in biomedical and biotechnology areas. For example, Ciencia is developing a prototype AOTF-based optical probe that may help to pinpoint certain types of heart disease by detecting unstable plaque in the coronary arteries.

In addition, radiofrequency generation technology developed under a BMDO SBIR for implementation of AOTFs is at the heart of the least expensive and most rapid fluorescence lifetime sensing system on the market. The system, called LifeSense™, is manufactured and distributed by Oriel Instruments (Stratford, CT).

HOW IT WORKS

Acousto-optic devices use ultrasound to alter the refractive index of an optical medium, typically a crystal. Ciencia developed an AOTF based on an organic amorphous material rather than crystals. Amorphous materials are easier and cheaper to make than crystals, allow for uniformity and quality control during manufacturing, and permit independent control of bandpass and bandwidth.

By the application of mechanical stress or electric fields, Ciencia's amorphous medium can be induced to exhibit birefringence, a type of refraction in which the speed of light through the material depends on direction as well as the light's frequency. Birefringence allows the AOTF to separate light into different colors. Unlike an ordinary monochromator, the AOTF can be tuned electronically, so it has no moving parts. In addition to being tunable, the polymeric device can produce spectrally resolved images.

MEDICAL SIGNIFICANCE

Optical Signatures. Recent studies suggest that the chemical composition of arterial plaque can indicate whether a person is likely to develop a blood clot. Ciencia's Raman-spectroscopy-based optical probe, coupled with the

AOTF can reveal whether a plaque contains destabilizing compounds, such as collagen or oxidized low-density lipoprotein (LDL, or "bad" cholesterol), that might raise the risk of clot formation. The filters help decipher the chemical signatures picked up by the probe, which would be inserted through an ultrasound-guided catheter into the arteries of the heart.

When developed, the optical probe can help to detect patients who are poor candidates for balloon angioplasty, which carries the risk of postprocedure clot development. An even more promising application of this technology is in optical biopsy, where a fiber-optic probe can replace the scalpel to detect cancer. For sites such as the lung and gastrointestinal tract, an optical probe can be used in tandem with established endoscopic techniques to identify abnormal cells without excising them.

Fluorescence Lifetime Analyses. Oriel Instruments is using Ciencia's technology as part of LifeSense, a device that detects the fluorescence lifetime signatures of organic compounds. For less than $20,000, Oriel's LifeSense system can be used for biological and environmental research.

In molecular biology, fluorescence lifetime sensing can unlock the secrets of the human genome, as well as observe molecular diffusion in cells, antibody-mediated reactions, and a host of intra- and extracellular functions. Researchers bind special fluorescent dyes to cell structures of interest, excite the sample with an appropriate wavelength, and observe the movement and distribution of critical macromolecules. LifeSense can also pick up the signatures of nontreated cells and tissue via native fluorescence.

VENTURES OR PRODUCT AVAILABILITY

The cardiovascular applications of Ciencia's technology are under assessment.

Oriel's LifeSense performs real-time analysis with Windows-based software on a 486 or Pentium PC and provides measurements in 1 second. The high-sensitivity, high-resolution instrument has interchangeable LED or laser light source modules and is suitable for commonly used dyes such as fluorescein, rhodamine, and phycocyanin. In addition, its compact size and light weight make it a convenient benchtop system.

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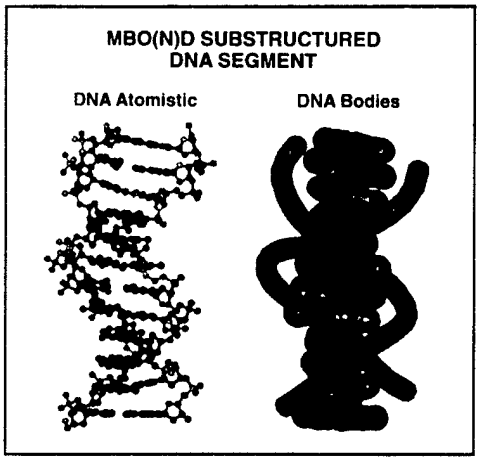
HIGH-SPEED MOLECULAR MODELING



● *Molecular modeling can greatly speed up decision making in drug selection strategy.*

In the immune system, the shape of an invading pathogen and the "memory" of the immune system for this shape help dictate whether a person acquires an infection, fights off the infection, or develops an autoimmune disease.

BMDO HISTORY

With the help of BMDO contracts to simulate the mechanical behavior of large space-based structures, Photon Research Associates (PRA; San Diego, CA) has developed a computer algorithm that reduces the time needed to model the dynamics of large molecular systems. In the early to mid-1980s, PRA developed multibody modeling technology to simulate the dynamics of large space-based structures. The original sponsors of this research included the Defense Advanced Research Projects Agency and NASA. Tests of the algorithm, called MBO(N)D, have shown that it can simulate the dynamics of large molecules (10,000 atoms) up to 50 times faster than conventional all-atom modeling techniques, while maintaining accuracy in the essential dynamics. Applications to larger molecules (10,000 to 100,000 atoms) and further refinements to the algorithm should make it about 100 to 1,000 times faster than all-atom approaches.

HOW IT WORKS

MBO(N)D accelerates computational speed while maintaining a great deal of chemical and physical realism. This achievement is possible through a technique known as "substructuring," which combines atoms into interacting groups of rigid and flexible bodies. The algorithm also filters out high-frequency motions that do not affect the overall behavior of the molecule. These two innovations reduce the number of system variables and allow the simulation to be computed over a smaller number of time steps.

MEDICAL SIGNIFICANCE

Drug discovery has changed over the past 15 years to include the study of significant structural components in and around the cell. Molecular structures of proteins and receptor-ligand complexes play an important role in the discovery of novel agents. A ligand is a biological compound that fits a receptor within or on the cell surface in a "lock and key" arrangement. Drugs that mimic the shape of the natural ligand can be used to up- or down-regulate a signal that is transduced by the cell receptor. Some receptor structures are found by x-ray crystallography, some by nuclear magnetic resonance, and some by homologous comparisons to similar structures. All of these techniques rely on molecular dynamics to find the correct positions of all the atoms in the drug and the receptor and how they move to interact with each other. While highly parallel supercomputers

(like those of Cray and IBM) have increased the number of structures resolved and modeled the molecular dynamics motion of drug and receptor in the nanosecond range, this brute-force method has not brought these capabilities to the drug discovery desk.

By increasing computational speed, MBO(N)D can improve on the all-atom technique and can make predictive modeling, the discovery of new drugs, and the development of new materials through computational techniques more practical. Drug development is a major risk for pharmaceutical companies, often requiring at least a decade of development and many millions of research dollars. Molecular modeling stands to considerably improve the risky environment in which this type of research takes place.

VENTURES OR PRODUCT AVAILABILITY

In 1991, PRA formed a subsidiary called Moldyn, Inc. (Cambridge, MA), to further develop and market the MBO(N)D technology for the molecular dynamics applications mentioned above.

In 1994 Moldyn received an Advanced Technology Program award from the National Institute of Standards and Technology to help bring the technology to the pharmaceutical industry. In this project, Moldyn and its partners have been refining the MBO(N)D algorithm for commercial use. Moldyn's partners in this project include leading pharmaceutical companies (Bristol-Myers Squibb, Vertex Pharmaceuticals), a commercial computational chemistry software firm (Molecular Simulations, Inc.), and leading academics in computational chemistry.

Moldyn has received one patent covering a molecular dynamics simulation method and apparatus based on the MBO(N)D algorithm and has copyrighted the MBO(N)D code.

The MBO(N)D software will be marketed and distributed by Molecular Simulations, Inc., which has partnered with Moldyn to incorporate MBO(N)D within one of Molecular Simulations' most popular graphic user interfaces, Insight. The code can also run in stand-alone mode. Academic release of MBO(N)D is expected in 1998. Moldyn also plans to market services using MBO(N)D directly to pharmaceutical companies.

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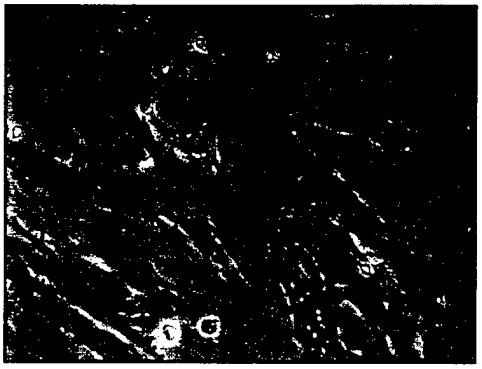
LiSAF LASER FOR CYTOMETERS



● *Compact laser technology can help improve flow cytometry.*

Cell sorters or cytometers have become very sophisticated in a short time in part because of the enormous demand that creative biologists have brought to bear on the industry. Advances in lasers, coupled with newly available dyes and ever-increasing antigen-antibody combinations, have played a large part in widening the range of cell types that can be identified with cytometers.

BMDO HISTORY

A new diode-pumped solid-state lithium strontium aluminum fluoride (LiSAF) laser is being developed by Science and Engineering Services, Inc. (SESI; Burtonsville, MD). It will provide simultaneous output wavelengths of 490 and 980 nanometers. The Q-switched laser is based on a LiSAF crystal, doped with chromium. The short laser pulse durations and solid-state nature of the laser contribute to the system's low power consumption, compactness, and reliability under severe vibrational stress and wide temperature variation. BMDO has provided Phase II funding for this effort, with matching funds provided by the Army and Recon Exploration (Dallas, TX). BMDO has also funded the development of frequency-agile lasers for spaceborne spectroscopic platforms, LIDAR, tracking, detection of atmospheric constituents, and detection of wind shear. SESI has performed research with NASA, the Army, the Navy, and the National Science Foundation in the areas of atmospheric sensing, LIDAR, general laser development, and novel medical instrumentation.

HOW IT WORKS

The laser is tunable within a fundamental range of 780 to 1,000 nanometers and has a high repetition rate (1 to 2 kilohertz) and microjoule pulse capability (50 to 80 microjoules). SESI plans to couple the LiSAF laser system to a flow cytometer to make it more reliable than cytometers operated with non-solid-state, continuous-wave laser outputs. A flow cytometer is a device that uses a laser to detect the fluorescence intensity of cells that flow past a detector in a thin stream. If fluorescence is detected, the cell is given an electrical charge and deflected into a collection bin. The simultaneous output of two different wavelengths can expand a cytometer's ability to sort multiple cell types during one sorting run. By frequency doubling, the second harmonic of the laser can provide blue-green activity, tunable from 390 to 500 nanometers, that would be valuable in the communications

field. A third harmonic bandwidth of 260 to 330 nanometers is possible with further development and would be applicable in ultraviolet flow cytometry. The ultraviolet wavelengths might prove especially useful in lighting up DNA and determining stages in the cell cycle, for example.

MEDICAL SIGNIFICANCE

There is a very large market in biotechnology and medicine for flow cytometers. Among their uses are cell sorting by chromosome content, infective status, antigen presence (as in determination of tissue transplant compatibility), and cell-receptor-ligand combinations. They are used in both research and clinical institutions to analyze a large variety of cell types and can identify cell characteristics through native fluorescence or dye-based illumination strategies.

VENTURES OR PRODUCT AVAILABILITY

SESI is working to commercialize its LiSAF laser and is currently retrofitting a cell sorter manufactured by a well-known flow cytometer supplier.

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SECTION C
DIAGNOSIS

Ancient Chinese medicine held that the gallop of the pulse reflected the state of the body, and practitioners used the intricate patterns of the heartbeat to confirm many diagnoses. In the age of technology, patterns also hold clues to the status of the organism. Two techniques used in adaptive optics technology, originally developed to discern wavelength patterns in the scattering atmosphere, can remotely diagnose eye disorders. Vibrational spectroscopy can both visualize and quantify biochemical species in unstained cell samples. Applications in both spectroscopy and luminescent materials have led to devices that can detect airborne contaminants, cancerous cells, bioluminescent signatures of bacteria, and specific gene sequences. Even ultraprecise gimbal technology derived from laser communications research has found a place in a needle biopsy system.

1. A wavefront sensor that can process data on astigmatism, interpupil distance, and ocular accommodation and can do so over telemedical routes.

2. A deformable mirror that improves retinal imaging for the study of photoreceptors in the eye.

3. An infrared array that is the heart of a microscope that can visualize and quantify silicone leakage in breast tissue.

4. A multispectral sensor that analyzes biological material in three dimensions.

5. A combination spectrometer-endoscope that helps doctors diagnose oropharyngeal cancer.

6. A nonradioactive, nonfluorescent gene probe that distinguishes double-stranded DNA from single-stranded DNA.

7. Nanocrystals that emit visible light when excited by infrared wavelengths and have potential as molecular tags.

8. A spectroscopic method that reveals true-color images of cancerous versus normal tissue.

9. A robust, extremely accurate driver for guided needle biopsy of the breast.

AMT: BINOCULAR 3-D EYE TRACKER

● *A novel wavefront sensor can help doctors remotely diagnose eye disorders.*

While our view of the world may seem smooth and uninterrupted to us, the continual, jerky movements of the eye are essential to maintaining this clear image. Paradoxically, if these eye movements are artificially stilled, the world becomes a defocused blur.

BMDO HISTORY

Applied Modern Technologies Corporation (AMT; Huntington Beach, CA) has developed an eye-tracking device based on wavefront sensor technology borrowed from adaptive optics. In the 1980s, BMDO focused much attention on how light, particularly high-energy laser light, was propagated through the atmosphere. This interest generated a host of techniques to correct the scatter of light in turbulent air, improving both transmission and detection of light. The astronomy field has benefited greatly from advances in adaptive optics—for example, using it to remove the "twinkle" from galactic objects—but other areas of science are also reaping the rewards of this technology. AMT's Ocular Vergence and Accommodation Sensor (OVAS) is a new product for the vision sciences and medical research that can trace its lineage to BMDO adaptive optics technology.

HOW IT WORKS

OVAS uses two low-power (1.25 milliwatts per square centimeter; eye-safe) infrared laser beams that are reflected from each eye's retina. The reflection provides information about the movement of the eyes and other biometric data that can be processed and used for a variety of applications. AMT's design includes a 12-component optics system and a Pentium processor with algorithms for processing data on the accommodative state, movements, and vergence of the eyes, as well as 10 other ocular functions.

MEDICAL SIGNIFICANCE

Telemedicine. OVAS could provide diagnostic data from a patient to a doctor many miles away. The application to soldiers in the field includes early detection of exposure to chemical warfare agents. The AMT system is rugged enough for battlefield conditions and can be miniaturized for integration into a portable, head-mounted system. OVAS is proposed as part of a testbed project for remote ophthalmic instruments for the Tripler Army Medical Center. The center's responsibilities include health care for the U.S. South Pacific Protectorate. Doctors are scarce on these small islands, and often the citizenry and military personnel must make do with limited immediate medical care. With OVAS, an ophthalmologist at a remote location may be able to evaluate a Tripler patient's eyes for corrective eyewear and for such conditions as cataracts and diabetic retinopathy.

The South Pacific population experiences a very high rate of diabetes-related blindness.

Ophthalmology and Optometry. OVAS is an automated system that can determine prescription lens strength, astigmatism, interpupil distance, and accommodation. Because OVAS is binocular, both eyes are measured simultaneously. AMT feels this is superior to the current practice, which measures each eye separately. Potentially, lens prescriptions could be balanced to reduce the dominant-eye effect now common for corrected vision. Future units can be used to precisely measure the minute aberrations of the cornea, helping to fit contact lenses or to determine the depth of abrasions. In surgery, OVAS could identify astigmatism introduced by the surgery and allow immediate correction. The benefits extend to school children for a quick, accurate eye-screening device and to faster, more in-depth eye exams requiring no feedback from the patient.

Other Medical Applications

For those who are paralyzed or seriously restricted in their ability to move, eye movement sensors have been in use for some time. With an "ocular mouse," the user can look at an icon or array of letters on a monitor to initiate a program function or spell out words. These assistive computer interfaces add immensely to the quality of life of such individuals, and sensors that can accurately track eye movement are crucial to the technology.

Medical students, residents, and interns are taking increasing advantage of virtual reality (VR) for educational purposes. Surgical trainees can now practice such procedures as laparoscopies on a VR simulator before moving on to real patients. VR also needs eye movement and focusing information for its next-generation products.

VENTURES OR PRODUCT AVAILABILITY

AMT has applied for 89 patents related to OVAS and is marketing a research version of OVAS aimed at the medical market. This includes studies where OVAS' data points are used for statistical analysis and include vision research, neuro-ophthalmology, display research, VR research, and scene generation. OVAS is suitable for office, laboratory, or mobile use.

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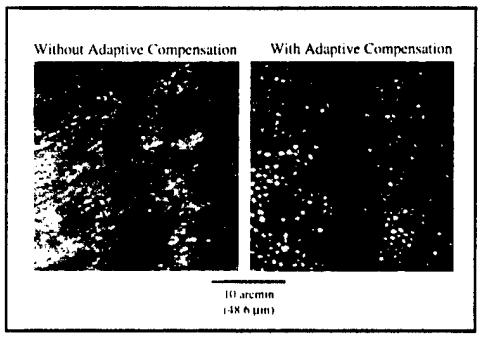
DEFORMABLE MIRRORS TO UNCOVER EYE DISORDERS



● *Deformable mirrors help researchers take a closer look at diseased retinas.*

Approximately 80 percent of premature infants weighing less than 1 kilogram at birth will develop retinopathy of prematurity (ROP). Children with ROP are diagnosed with retinal scarring, nearsightedness, and crossed or "wandering" eyes at a much higher incidence than normal-weight infants.

BMDO HISTORY

Xinetics, Inc. (Littleton, MA), is using adaptive optics technology developed for BMDO to bring optical correction and precision to a medical imaging application. BMDO funded the original research primarily for the ground-based free electron laser, whose beams were subject to atmospheric distortion. With research and development funded by BMDO, the U.S. Navy's Office of Naval Research, and the U.S. Air Force's Phillips Laboratory, Xinetics' core team developed lead magnesium niobate (PMN) actuators and deformable mirror technology at Itek Corporation and United Technologies Optical Systems.

HOW IT WORKS

Adaptive optics is an aggregate technology that analyzes the characteristics of light waves and minimizes their distortion. The two principal corrections are for the "tilt" of the light entering the optical system and for the light scatter caused by collisions with molecules in the atmosphere or in the vitreous fluid of the eye, for example. An adaptive optics system uses a wavefront sensor to measure the optical distortion and supply a control computer with an error map. The computer then sends commands to a deformable mirror that changes shape to correct the distortion. Deformable mirrors use small piston-like devices called actuators to bend a thin sheet of polished ultralow-expansion fused-silica glass.

The key elements in the Xinetics deformable mirror technology are piezoelectric or electrostatic actuators based on PMN crystals. These actuators expand and contract when an electric field is applied, pushing and pulling the mirror sections into different shapes. PMN actuators are well suited to deformable mirrors because of their high stiffness, negligible hysteresis, and excellent stability. To produce PMN actuators in high volumes, Xinetics uses a layered ceramic process developed in the microelectronics and multilayer capacitor industries. The process eliminates conventional glue bonding to provide high stiffness. It also reduces operating voltage from 3,000 to 100 volts.

The South Pacific population experiences a very high rate of diabetes-related blindness.

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MEDICAL SIGNIFICANCE

A Xinetics deformable mirror is now part of a retinal camera being developed by David R. Williams, Ph.D., the director of the University of Rochester's Center for Visual Science. The camera already provides a twofold improvement in resolution over present ophthalmic imaging devices such as the fundoscope. The resolution of the retinal camera is currently 2 to 10 micrometers and is expected to eventually reach 0.3 micrometers. The camera can provide detailed images of photoreceptors in the retina and can detect early changes in disorders like diabetic retinopathy and retinitis pigmentosa. It can also be used to more precisely measure refractive error (the degree of nearsightedness or farsightedness) in the eye. Microaneurysms, or small balloon-like lesions of capillaries, can also be diagnosed. Microaneurysms can reflect the presence of more serious blood vessel disorders in the brain. Developmental progress of neonatal eyes can also be tracked with this device. Retinopathy due to oxygenation of immature retinal cells is an increasing problem in premature infants, particularly as gestational age at birth decreases.

VENTURES OR PRODUCT AVAILABILITY

Xinetics, a 15-person company founded in 1993, makes custom and standard adaptive optics technologies for military and commercial customers. The company is engaged in a number of agreements to manufacture deformable mirrors and actuators for medical applications, astronomical telescopes, optical scanners, and micropositioners.

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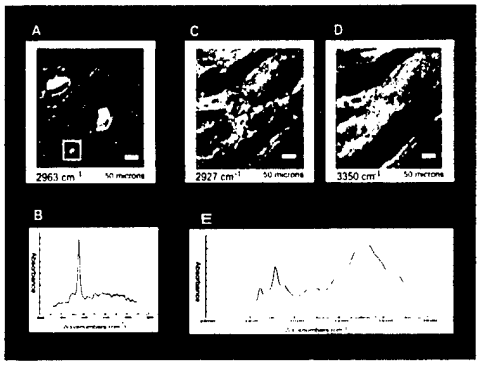
NIH INFRARED MICROSCOPE



● *This novel microscope dramatically and specifically highlights cell constituents.*

The furor over silicone breast implants is far from resolved. Epidemiologists are pitted against cytopathologists, many of whom read different patterns in the available evidence. It is clear, however, that silicone leakage into living tissues is a highly undesirable event.

BMDO HISTORY

E. Neil Lewis, Ph.D., and a group of researchers at the National Institutes of Health (NIH) have developed an infrared microscope that uses a focal plane array (FPA) to obtain both spectral images and signatures of biological and other materials. The group used an indium antimonide (InSb) FPA for their initial work, in which they imaged silicone inclusions in paraffin-embedded breast tissue sections. Through an alliance with Ted Heilweil, Ph.D., a researcher at the National Institute of Standards and Technology (NIST), the NIH team was able to access a mercury cadmium telluride (HgCdTe) FPA from BMDO's Exoatmospheric Kill Vehicle program run by the U.S. Army Space and Strategic Defense Command at Huntsville, AL. The array is manufactured by Hughes and in this case did not meet military specifications. The researchers say that the few dead pixels on the array do not in any way affect the quality of their data. The HgCdTe array will enable the group to expand the microscope's wavelength range.

HOW IT WORKS

The NIH group collaborated with colleagues at NIST to extend the microscope's spectral range to 11 micrometers by using a BMDO-funded 256 x 256 HgCdTe FPA. The InSb FPA limits the microscope to the 2- to 5-micrometer range. Therefore, with the use of the HgCdTe FPA, it is possible to expand the number of spectral signatures that the microscope can detect, thereby greatly extending its chemical imaging capabilities. Both the InSb and the HgCdTe FPAs are nitrogen cooled.

Lewis developed the software that enables the acquisition and processing of the enormous amount of data that this microscope acquires. The microscope uses an interferometer to record spectra, and therefore the software uses Fourier transform techniques to convert the data to chemical images and spectra. Typically, each image data set contains 16 to 20 megabytes of data, although standard PCs are used to manipulate and store the data.

MEDICAL SIGNIFICANCE

Most components of living matter have a unique infrared signature that can be detected spectrographically. Molecular biology contributes new data almost every day about the molecular makeup of human beings and the significance of these molecules in health and disease. From cancer research, for instance, we know that abnormal proteins result from mutations in critical genes that govern cell growth. Proteins such as prostate-specific antigen; the breast-cancer-associated genes BRCA1, BRCA2, and HER2; and many others may one day be detectable in minute quantities by their infrared signatures. The ability to image molecular information from histological sections makes this instrument an especially qualified candidate for use in the pathology laboratory. In general research, the microscope's uses can be as varied as the researcher's interests.

Lewis and his group clearly demonstrated the presence of silicone inclusions in breast tissue samples and published their results in *Nature Medicine* (February 1997). Virtually all silicone gel breast implants have shown a tendency to rupture and bleed their contents into surrounding tissues. These leaks have also been known to migrate into distant organs. As a diagnostic tool in this controversial area, the microscope will enable clinicians to identify leakage from silicone breast implants visually and by chemical signature.

Many other industries are also interested in this technology. Polymers, pharmaceuticals, cosmetics, and semiconductors are just some of the items that can be analyzed with this microscope.

VENTURES OR PRODUCT AVAILABILITY

Lewis has generated interest from a number of Fortune 500 companies, including Procter & Gamble, Miles Laboratories, ICI, and Estee Lauder. Procter & Gamble has installed such an imaging system in collaboration with NIH, which owns the patent on the technology.

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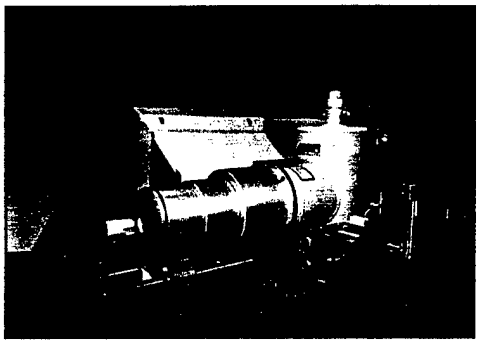
ADVANCED IMAGING SPECTROMETER



● *The IMSS imaging device can help detect bioluminescence in dangerous bacteria.*

Bioluminescence, a trait found in the familiar firefly, is a natural phenomenon that has enabled biologists to develop clever ways to track gene expression in animals. For instance, a glowing protein found in jellyfish has been successfully incorporated as a reporter gene in transgenic laboratory mice.

BMDO HISTORY

Pacific Advanced Technology, Inc. (PAT; Solvang, CA), has developed an imaging spectroradiometer that can be used to detect and identify chemicals and biological matter for military, environmental, law enforcement, and medical applications. Called the image multispectral sensor (IMSS), this technology is based on advances in diffractive optics and image and signal processing. It images a scene in three dimensions, two spatial and one spectral, to build a multispectral spatial imaging cube of data.

BMDO funded PAT's multispectral sensing technology in 1995 through the SBIR program in a joint project with Amber, a Raytheon company (Goleta, CA). Amber and BMDO provided $150,000 each for the project. With IMSS technology, BMDO could detect theater missiles in clutter, identify friend or foe, and detect and identify chemical agents. PAT previously obtained a BMDO SBIR Phase I contract outside this teaming arrangement.

HOW IT WORKS

While other spectral imaging devices have very complex optics and require exact alignment, PAT's instrument uses a simple optical design that allows for relaxed tolerances on optical alignment. Rugged and portable, it can operate in harsh environments such as airborne and space-based platforms.

PAT has commercialized this instrument with joint funding from the BMDO SBIR program and Amber. Amber sells the commercial IMSS as an attachment to its RADIANCE 1 and Galileo cameras to make a midwave infrared multispectral radiometric imager, useful for spectroscopy and radiometry. PAT supplies Amber with the multispectral lens system as well as the image- and signal-processing software called HYPAT. This system uses an f/2.5 nominal 102-millimeter focal length lens and covers the full 3- to 5-micrometer spectral band with a spectral resolution of less than 0.01 micrometers. Using the Galileo camera in the highest data acquisition mode, spectral images over the 3- to 5-micrometer band with 400 spectral bins can be collected in less than 1 second.

MEDICAL SIGNIFICANCE

PAT's multispectral imaging device is an ideal instrument for collecting optical signatures from biological matter, whether the task is to identify bacteria or a cancerous lesion. Bioluminescence systems are already in use for rapidly detecting the presence of *E. coli*, for example, in foodstuffs. For identifying cancers without surgical sampling of the suspicious area, optical biopsy is very close to clinical adaptation in a number of institutions. The IMSS can also be used for reading the optical signatures of tumors and for localizing them in a 3-D image. The device has an adaptive spectral filter that can separate excitation light from emission light; this is critical for the fiber-optic system that both delivers and collects light in the optical biopsy system.

If the capability of the IMSS is extended to longer wavelengths, the technology can be used to detect and identify chemical agents, such as sarin and other nerve gases. Through an Air Force SBIR Phase II contract, PAT is designing a system that will detect signatures at longer wavelengths for chemical warfare applications.

VENTURES OR PRODUCT AVAILABILITY

PAT is a woman-owned small business focused on electro-optic research and development. The company has one patent on the IMSS technology. PAT supplies its lens product to Amber, which has sold two RADIANCE 1 systems with the lens for military use. Another order is pending. Systems including the Amber camera cost roughly $70,000.

With the IMSS technology, Amber and PAT are focusing on applications to remotely monitor smokestack emissions and, in 1995, demonstrated promising results in the field. From 1 kilometer away, PAT's system detected carbon monoxide, carbon dioxide, and hydrocarbons from two smokestacks at an oil refinery. PAT is interested in demonstrating its technology to detect sulfur dioxide for environmental applications.

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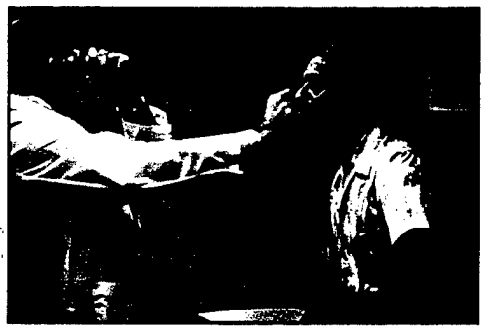
MTC's ENDOSCOPE



Courtesy of Beckman Laser Institute.

● *MTC's endoscope will be used in cancer drug trials in 1998.*

Cancers of the mouth and esophagus are largely preventable through lifestyle changes such as smoking cessation and limited alcohol use. It is imperative to catch the disease early to prevent development of potentially disfiguring and life-threatening lesions.

BMDO HISTORY

Another beneficiary of the BMDO-funded Medical Free Electron Laser (MFEL) program was Robert Alfano, Ph.D., at the City College of New York (New York, NY). Alfano is a physicist who has studied the optical properties of living tissue for a number of years. His recent work in visible light transmission through breast tissue has attracted considerable attention. Early in the MFEL program, however, Alfano experimented with the native fluorescence of tumor cells as compared with their normal counterparts. Fluorescence spectroscopy is an up-and-coming technology that is widely expected to become an integral part of cancer diagnosis within the next few years. Along with Mediscience Technology Corporation (MTC; Cherry Hill, NJ), Alfano devised an endoscopic tool that could be inserted into the mouth and esophagus to look for signs of cancer as determined by the fluorescence signature of the mucosal lining. This tool, the CD-Scan and CD-Ratiometer, will be evaluated in a major clinical trial at the Memorial Sloan-Kettering Cancer Center in New York City.

HOW IT WORKS

MTC's devices use a fiber-optic probe to illuminate tissue with a laser or other light source and a spectrometer to analyze the fluorescence that results from the illumination. Increasing numbers of investigators in oncology are finding that there are discernible and very useful differences between malignant and normal tissue fluorescence signatures. Trials such as those described below are necessary to correlate these signatures with conventional microscopic means of cancer diagnosis to create a useful clinical database. Consistent results that match fluorescence signals with cancer evidence mean that some future biopsies will be performed with light rather than scalpels. This database is growing significantly.

MEDICAL SIGNIFICANCE

In a previous report, we noted that MTC was planning an investigational device exemption (IDE) application for its device, which it obtained in early 1997. Stimson P. Schantz, M.D., an otolaryngologist at Sloan-Kettering who specializes in cancers of the head and neck, is using the CD-

Scan and CD-Ratiometer as part of his patients' clinical evaluations in a Phase II drug trial. A new and promising vitamin A derivative, 13-cis-retinoic acid, is being tested as a treatment for oral leukoplakia, a whitish lesion of the mouth that can progress to cancer. The CD-Scan will be used to corroborate excisional biopsy findings with the unique fluorescence signal of the precancerous lesion. The device will also be used in a Phase III trial that will follow the completion of the Phase II trial.

In addition, the U.S. Army Medical Research, Development, Acquisition, and Logistics Command will be using a fiber-optic needle and the CD-Ratiometer to diagnose breast cancer via needle biopsy techniques. As in Schantz's trial, the device will be used along with conventional histopathology methods to determine the fluorescence signals associated with breast malignancies. This trial will be conducted at Massachusetts General Hospital (Boston, MA). The principal investigator is radiologist Daniel B. Kopans, M.D.

MTC is also planning to file an IDE for detecting gastrointestinal premalignancy with the CD-Scan device.

VENTURES OR PRODUCT AVAILABILITY

MTC has 15 patents in the area of biomedical optics. The CD-Scan and CD-Ratiometer are based on its patented tissue fluorescence technology. MTC is also working with the City University of New York and General Electric to develop a non-ionizing optical mammography system, although optical techniques for this application are in the very earliest stages of development. MTC has received private equity financing from Allen and Company, an investment banking company, to carry out its research activities.

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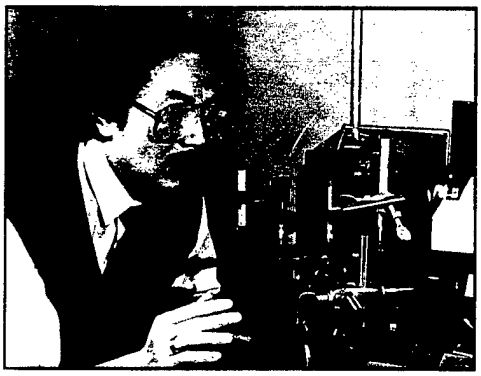
RAMAN-BASED GENE PROBE TECHNOLOGY



● *Dr. Vo-Dinh's nonradioactive, nonfluorescent gene probe is safe and sensitive.*

Since the race to sequence the human genome began, about 20 percent of human genes have been at least partially sequenced. However, scientists have identified functions for only 3 percent of the postulated 80,000 to 100,000 genes.

BMDO HISTORY

With the help of funding through BMDO's Innovative Science and Technology Directorate and the Department of Energy, an advanced optical technology called surface-enhanced Raman optical data storage (SERODS) was born. Developed to greatly expand data storage capabilities beyond those achievable with conventional silicon technology, SERODS also spawned a novel gene probe technology, SERGen. SERGen requires no radioactive tags or special fluorescing dyes and cuts gene identification time drastically, from as many as 16 hours to a matter of minutes. It can also be used with conventional molecular biology techniques such as polymerase chain reaction.

HOW IT WORKS

Surface-enhanced Raman spectroscopy (SERS) is the basis for SERGen's ability to distinguish between single-stranded and double-stranded DNA. Adsorbing a gene sequence of interest onto an "enhancing" microstructured metal surface greatly strengthens the Raman signal, allowing a researcher to detect minute quantities of specific DNA sequences with a spectroscope. When a gene sequence of interest is introduced into the reaction, the SERS probe seeks out its complementary partner on the reaction plate; this process is known as hybridization. Hybridization indicates that a match has been made between two complementary strands of DNA. The double-stranded hybrids give a unique Raman signal, distinguishing them from the single-stranded, unmatched sequences.

MEDICAL SIGNIFICANCE

There are many areas in which SERGen would prove useful because of its rapidity and sensitivity. For example, in our era of increasing antibiotic resistance, SERGen may prove a boon to doctors who want to quickly identify resistant organisms. In this way, the proper medication can be prescribed and a wasted course of ineffective antibiotics can be avoided. There are many known resistance genes in bacteria. With a simple probe that represents the sequence of the resistance gene, SERGen can immediately identify this unique biochemical tag to narrow drug treatment choices.

SERGen has already been used in the laboratory to detect sequences from the genomes of HIV-1, hepatitis B, and *Mycobacterium tuberculosis* (the organism that causes tuberculosis). Therefore, SERGen can serve as a fast probe for diagnosing infections without the long wait for cultures or antibody assays.

A much more newsworthy application of SERGen is in the Human Genome Project, for which discussions are under way. Gene sequencing and identification timetables have accelerated impressively; however, these incremental improvements have been variations on a few themes of conventional molecular biology techniques. SERGen could offer a drastic improvement in methodology.

VENTURES OR PRODUCT AVAILABILITY

SERGen won a 1996 R&D 100 award, and a patent for the technology is pending.

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NANOPHOSPHORS

● *Nanophosphors may someday be used to tag genes in chromosomes.*

The late, great physicist Richard Feynman was a vocal proponent of nanotechnology. With such technology, he once declaimed, the complete contents of the Encyclopedia Britannica could be written on the head of a pin.

BMDO HISTORY

Structured Materials Industries, Inc. (SMI; Piscataway, NJ), collaborating with Rutgers University, developed a deposition and processing technology to form, control, and study a variety of nanocrystal powders and nanostructured films, several of which are luminescent when in the nanocrystal structure. After conducting preliminary research into porous silicon and germanium nanocrystal structures with BMDO SBIR Phase I funding in 1992, SMI received Phase II funding in 1993 to continue the nanophosphor research. SMI has demonstrated luminescence from several nanocrystals and is pursuing full-color electroluminescent displays (ELDs). Recently, SMI demonstrated luminescence from several doped-oxide compounds as well. With the help of two additional BMDO STTR awards, and with the Massachusetts Institute of Technology and Lawrence Livermore National Laboratory, SMI is also developing an annealing technology for phosphors on glass, as well as zinc oxide epitaxy. Two more Phase I awards support development of p-type transparent conductors and nanostructured films, and a Phase II award supports alternative conductive and transparent oxides. A Phase II STTR contract supports nanopowder development.

HOW IT WORKS

A new patented, dry chemical-vapor-condensation process that can be customized for each particular type of nanoparticle is being marketed by SMI's new division, Nanopowder Enterprises, Inc. (NEI). The reactant chemicals are fed into the system on an inert carrier gas and then pass through a heated reaction chamber. During the reaction phase, the by-products dissipate as vapors. This leaves only the desired product: the dry, nonagglomerated nanoparticles. The condensation of the nanoparticles from the superheated, supersaturated vapor in the reaction chamber is so rapid that the particles do not have a chance to agglomerate. This rapid condensation produces nanoparticles with a narrow size distribution. The particular compound's chemistry is controlled by selecting an atmosphere that is oxidizing, reducing, carburizing, or nitridizing, as required. Multicomponent or multiphasic particles are formed by using multiple chemical reactant sources. This method controllably produces nanopowders from 3 to 50 nanometers in size. When materials are restricted to this small size, they

can have dramatically different properties from their larger counterparts. Some materials' strength approaches the calculated theoretical limit; some ceramic and intermetallic materials exhibit ductility, a property usually seen only in metals; some exhibit superplasticity; some exhibit quantum confinement effects; and some exhibit dramatically enhanced magnetic, electronic, and optical properties.

MEDICAL SIGNIFICANCE

Nanocrystal light emission has other uses besides ELD componentry. NEI is exploring other, more efficient nanophosphors that are brighter at lower excitation voltages and in each primary color: red, blue, and green. The nanophosphors are electroluminescent at 1000 volts and are brighter than standard CRT phosphors at that voltage. A promising biotechnology application for nanophosphors is molecular tagging to "up-convert" infrared radiation to visible photoluminescence. Laboratories now use tagging compounds that luminesce when exposed to either visible or ultraviolet light—shorter wavelengths that can destroy the sample material quickly. Using the up-converting nanophosphors to tag and visualize the DNA, for example, may provide an advantage because the nanophosphors are activated by infrared light, which is less destructive than ultraviolet or visible light. With three colors, researchers can choose from or combine the nanophosphors to create a wide-range spectrum for identifying different molecules such as specific DNA sequences or cellular proteins.

VENTURES OR PRODUCT AVAILABILITY

Founded in 1993, SMI established NEI as a division in 1995 specifically to manufacture and market nanocrystalline materials, Nanomyte™ powders, and Nanomyte One™ processing equipment. NEI has received patents and has patents pending for the production method and apparatus for nanostructured ceramic powders and whiskers; the method for large-area deposition and processing of nanoparticle powders on sheet substrates; and for high-volume, low-pressure combustion flame synthesis of nanophase materials. SMI and NEI offer a variety of films, powders, and processing equipment and have generated several hundred thousand dollars in matching funds for these program areas.

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OPTICAL BIOPSY

● *Optical biopsy holds the key to early cancer diagnosis.*

BMDO HISTORY

Funding for surface-enhanced Raman optical data storage (SERODS) at Oak Ridge National Laboratory (ORNL) also led to a different sort of biological probe (see previous article on SERGen). Tuan Vo-Dinh, Ph.D., conducted studies with SERODS-associated lasers that have contributed to the use of lasers for a cancer detection method that substitutes light for the scalpel of surgical biopsy. Using the body's own emission in reaction to certain wavelengths of laser light, it is possible to detect unique fluorescence signals with a spectrometer. As demonstrated in studies conducted by Vo-Dinh at ORNL and his co-developers, Masoud Panjehpour, M.D. and Bergein Overholt, M.D., at the Thompson Cancer Survival Center (Knoxville, TN), this activity can demonstrate cancerous "hot spots" without removing tissue. Optical biopsy, as this technique has come to be known, has gained tremendous momentum within the last two years. Major trials are under way in many U.S. cancer treatment centers, such as Memorial-Sloan Kettering (New York, NY), Roswell Park (Buffalo, NY), Wellman Laboratories of Photomedicine (Boston, MA), and Beckman Laser Institute (Irvine, CA).

The average age of a cancer patient at diagnosis is 60; this fact probably reflects long-term exposure to environmental insults and carcinogens, as well as the aging body's declining ability to repair genetic mutations.

HOW IT WORKS

The tissue under investigation is illuminated with laser light via a fiber-optic probe. Electrons in the tissue are temporarily kicked into a higher quantum state, or energy level; when they relax to a lower energy level, photons are emitted for a short time (fluorescence). A spectrometer records the wavelength of the fluorescence. Cancerous tissue fluoresces at peak wavelengths different from those seen in normal tissue. By comparing the peak readings, the fluorescence signatures can be converted into a real-color image that shows precisely where normal tissue ends and cancerous tissue begins. This method is also sensitive to precancerous changes and inflammation.

MEDICAL SIGNIFICANCE

Early diagnosis is the key to effective therapy and long-term cancer survival. Optical biopsy can help to diagnose cancers before they have had a chance to spread and can also alert the clinician to precancerous conditions that can thereafter be carefully monitored. Slender fiber-optic light delivery can also reach hard-to-access regions, can be used with conven-

tional endoscopy, and is minimally invasive. Visual confirmation of a tumor before surgery can prevent tumor excision that is too wide of the mark—often, clinicians remove extra margins around the primary tumor to ensure that no cancerous tissue has been left behind, with results that are disfiguring.

VENTURES OR PRODUCT AVAILABILITY

Vo-Dinh's optical biopsy method, BiOptics, has been licensed to Optical Biopsy, LLC, a joint venture of Venture Alliance (Knoxville, TN) and Pioneer Surgical (Loxahatchee, FL). The technique is being evaluated at the Thompson Cancer Survival Center in cancers of the esophagus. More than 100 patients have been studied, with a detection rate of 98 percent. In addition, the BiOptics technology won a 1997 award from the American Museum of Science and Energy.

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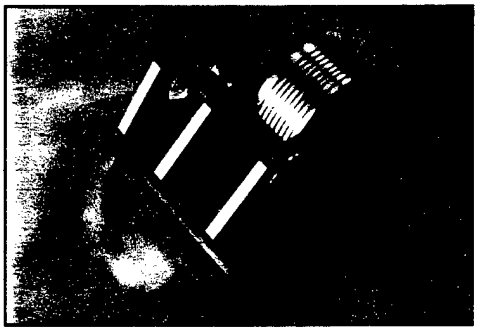
SAGEBRUSH GIMBAL FOR NEEDLE BIOPSY



● *The Roto-Lok rotary drive helped Fischer Imaging make a better needle biopsy device.*

Needle aspiration cytopathology was originally developed in the United States in the 1920s, but Scandinavian studies from the 1940s through the 1970s led to U.S. acceptance of the needle biopsy for breast tissue.

BMDO HISTORY

Sagebrush Technology Inc. (Albuquerque, NM) developed a novel rotary drive system to precisely position laser beam transmitters and receivers in a communications network. The device, called the Roto-Lok® rotary drive, has both military and commercial applications in the angular positioning of mechanical components. The Roto-Lok rotary drive was originally designed to control large, heavy astronomical telescopes. The BMDO Laser Communications (LaserCom) program, however, provided key support to develop the drive into a high-visibility product. In the LaserCom project, Sagebrush used the Roto-Lok drive to control the precision angular alignment of laser beam transmitters and receivers in a communications network. The drive also served to position a telescope on BMDO's High Altitude Balloon Experiment.

Fischer Imaging (Denver, CO) recently acquired a Roto-Lok drive to improve the accuracy of its needle biopsy guidance system, used to sample breast tissue. This adaptation has allowed Fischer engineers to provide accurate, smooth needle delivery to the region of concern.

HOW IT WORKS

The drive uses spring-loaded cables to accurately turn a cylinder (drum) that positions the equipment. The cables are wound around the drive motor shaft (a capstan) and attached by a spring at one end to the drum. As the capstan turns, friction from the cables forces rotation of the drum and the components mounted on it. The tensioned cables provide high torsional stiffness without backlash (a design problem in precision gears that reduces pointing accuracy and transmission efficiency). They also provide smooth operation. Because the cables do not slide on the drum or capstan, there is virtually no wear. Any imperfections on a single cable or on the drum are averaged over the multiple cables, so the drive is extremely smooth. In addition, performance does not degrade with use. The drive can position the drum to within 1 microradian of arc. Further, it transmits rotation at efficiency rates greater than 98 percent and runs more quietly than any other mechanical transmission system.

MEDICAL SIGNIFICANCE

Roto-Lok drives are now lending precision and reliability to Fischer Imaging's specialized needle biopsy driver. The device is a semiautomated ultrasound imager that displays the breast lesion and helps to position a needle for minimally invasive breast biopsy. The Roto-Lok drive enables the physician to aim and deliver the needle with great accuracy and smooth motion, which are of utmost importance in any biopsy. In addition, the driver's performance does not degrade with repeated procedures, significantly reducing overall maintenance. The simpler mechanics of the drive also allow for improved housing so that the unit is easier to manipulate and sterilize between procedures.

When a mammogram or self-exam reveals a suspicious area, needle biopsy is the least invasive way to sample the region of concern and yield a core of tissue for a histopathological examination. If the sample is positive for cancer, then mastectomy or breast-conserving lumpectomy may be performed, with adjuvant therapy. If the sample is negative, then the patient will have avoided more painful, costly, and cosmetically unsatisfactory surgical biopsy.

VENTURES OR PRODUCT AVAILABILITY

Sagebrush currently custom-designs Roto-Lok drives for a variety of applications. Sagebrush has received several patents for the Roto-Lok drive. Patent applications also have been filed. At present, Fischer is finishing its adaptation of the Roto-Lok drive into its needle biopsy unit.

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CHAPTER 3
INTERVENTION TECHNOLOGIES

When living systems fail because of disease or aging, medicine has at its disposal some truly amazing remedies. These nostrums range from outright replacement of the defective part, to modification of an existing one, to the general practice that most of us are familiar with. To effect these healing changes, a wide range of technology developments have been used. Microelectromechanical systems engineering, ion beam implanting techniques, new biocompatible materials, ultrashort electrical pulses, and lasers all play a part in these medical advances.

THIS CHAPTER INCLUDES THE FOLLOWING SECTIONS AND THEIR STORIES:

SECTION A
IMPLANTS

Hearts can be replaced, but only with a donation from another human being. Luckily, less vital parts can be strengthened or supplanted by artificial components designed to produce minimal reaction from the host. The exception in the following series of stories is a miniature inertial unit that may be worn on the outside of the body, but the remainder are variations on the theme of better materials for biocompatibility, based on modifying the surface and structural characteristics of the implantable object.

1. A vest fitted with sensors that can provide tactile feedback signals to persons with balance disorders.

2. Stronger material components for hip replacement surgery.

3. Lightweight orthotics for knee and leg braces.

4. An ion-beam method for increasing battery lifetimes for pacemakers, meaning fewer surgeries.

5. Inserts to stabilize the spine to ameliorate the pain of trauma or degenerative disease.

MEMS SENSOR FOR BALANCE DISORDERS

The lightweight MEMS sensor may someday act as a cue to patients with inner-ear disorders.

Vestibular disease can be detected by observing rhythmic movements of the eyes while instilling warm or cool water into the ears. In a normal subject, cool water causes the eyes to move in the opposite direction of the irrigated ear, and warm water causes movement toward it. The clinician can judge certain aspects of disease by watching how fast or how slowly the eye movements occur and whether movement is suppressed in a particular direction.

BMDO HISTORY

The Charles Stark Draper Laboratories (Cambridge, MA) developed a micromachining process for the manufacture of miniature inertial sensors using microelectromechanical systems (MEMS). The low-cost sensors combined the functions of a gyroscope and an accelerometer with an information processor to provide inertial guidance components for BMDO's Lightweight Exoatmospheric Advanced Projectiles program. The lightweight sensors have numerous applications in military and commercial technology, including precision-guided munitions, autopilot controls, airbag deployment, and medical electronics. In this last category, the micromachining innovation may lead to a unique way to help patients with balance disorders.

HOW IT WORKS

Draper Labs' micromachining process uses controlled chemical etching that can place up to 10,000 devices on a single silicon chip. The chips can be mass-produced, keeping production costs to a minimum. In addition, the low power requirements, small size, and complexity of the chip make it a versatile component for a lightweight feedback system. The chip's features have lent themselves well to a collaborative project involving the restoration of balance cues to patients with inner-ear disturbances.

MEDICAL SIGNIFICANCE

Vestibular (inner-ear) disorder is an uncommon but sometimes very debilitating condition that can be caused by transient viral infections, tumors, or trauma to the vestibular organs and nerves. Signals about the body's orientation in space (particularly rotational changes) are processed by a system of hair cells that are moved about by fluid flow within the inner ear's semicircular canals. These signals are relayed by the vestibular nerves to the brain, which in turn signals the body to make postural adjustments to maintain balance. Damage to the

vestibular system can cause some patients to lose their sense of balance, resulting in recurrent dizziness that can greatly inhibit lifestyle and cause injury. In February 1997, researchers at Draper Labs, the Massachusetts Eye and Ear Infirmary (MEEI), and the Massachusetts Institute of Technology (MIT), with the support of the W. M. Keck Foundation of Los Angeles, began to consider the MEMS chip as a component in a feedback loop system that alerts patients when they begin to lose their balance. An initial system design would incorporate MEMS devices into a vest that can be comfortably worn by a patient. When one of the MEMS chips senses a deviation of a few degrees from vertical (indicating that the wearer is falling), a vibration is induced that alerts the wearer to correct the situation. An arrangement of chips can take the place of normal cues provided by the ailing vestibular system. Eventually, researchers hope that such an inertial guidance device could be inserted in the inner ear itself, much as cochlear implants are implanted in deaf patients.

VENTURES OR PRODUCT AVAILABILITY

This nascent work is part of the Balance Project in the W. M. Keck Neural Prosthesis Research Center at Massachusetts General Hospital. The center includes investigators from MIT, MEEI, and Draper Labs. The center's director is Donald Eddington, Ph.D., of the Cochlear Implant Research Laboratory at MEEI. Draper Labs is contributing internal funding to this project as well.

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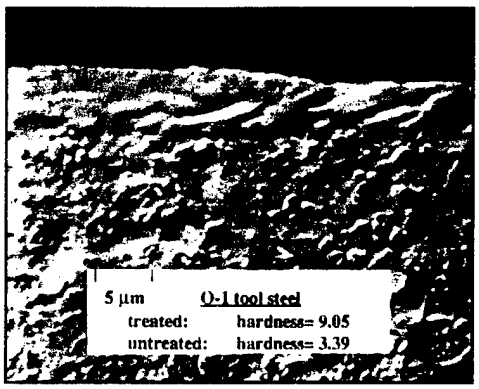
ION-BEAM SURFACE TREATMENT FOR IMPLANTS



IBEST can help strengthen the surfaces of weight-bearing artificial joints.

More than 90 percent of hip replacements last at least 10 years. This statistic is expected to improve as materials and techniques evolve further.

BMDO HISTORY

Sandia National Laboratories (Albuquerque, NM) developed an ion-beam treatment technique called IBEST™ (ion-beam surface treatment) to modify surfaces of metals, ceramics, and plastic to make them more durable. The repetitive high-energy pulsed-power (RHEPP) accelerator developed for this treatment was funded in part by BMDO's Free Electron Laser weapons program and the Department of Energy's Inertial Confinement Fusion program. IBEST does not produce environmentally harmful waste products or residue, unlike predecessor technologies such as electroplating and other chemical processes. To commercialize the patented IBEST technology, two Sandia scientists obtained exclusive worldwide rights to IBEST and formed a new company called QM Technologies, Inc. (Albuquerque, NM).

HOW IT WORKS

RHEPP accelerators deliver short-duration, high-intensity ion beams. This combination of rapid pulsing and high energy allows controlled melting and surface modification of various materials. The heart of the RHEPP accelerator is a magnetically confined anode plasma (MAP) diode, invented at Cornell University. Through this device, an electrical pulse is delivered to a pre-ionized gas inside the MAP diode. The electrical pulse kicks ions out of the plasma that then travel through a vacuum to the surface to be modified. The IBEST ion beam can cover several hundred square centimeters at once. Very thin surface layers (2 to 20 micrometers thick) are rapidly melted and cooled, forming nanocrystalline grain layers without changing the atomic composition of the treated surface.

MEDICAL SIGNIFICANCE

Medical implants, especially weight-bearing hip joints for replacement surgeries, need to be durable. The longer a joint remains functional, the longer the patient can avoid a second surgery to replace a failed or worn implant. Modern artificial hips are often made of composite material, usually a ceramic that is coated with a durable metal, such as titanium, at the femur head (the "ball" of the ball-and-socket hip arrangement). Minute cracks in the metal coating allow calcium ions from the synovial fluid (lubricating fluid in the joint) to migrate through to the composite material of the replacement, causing the material to break down. IBEST treatment can minimize or eliminate these cracks, resulting in a longer-lived joint.

VENTURES OR PRODUCT AVAILABILITY

QM Technologies is currently evaluating materials used by companies manufacturing artificial joints with an eye to improving knee and hip joints with IBEST technology. IBEST also has many applications in the nonmedical arena, with development projects in the automotive, aerospace, and tool-and-die industries.

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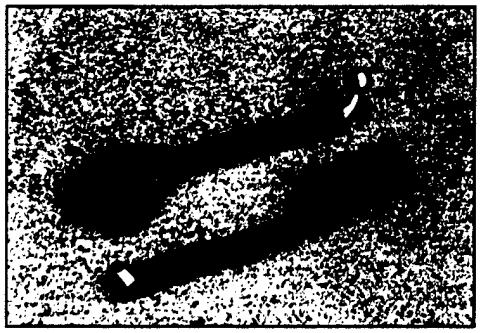
ADVANCED MATERIAL FOR ORTHOTICS AND IMPLANTS

BMDO HISTORY

SPARTA, Inc. (San Diego, CA), has developed composite materials for stronger, lighter-weight orthotics and medical implants. BMDO funded SPARTA's work in structural materials. The requirements for high stiffness and strength in a ground-based missile interceptor led to a composite material of graphite fiber and resin.



SPARTA's technology has been instrumental in improving hip, knee, and ankle joints.

Approximately 43 million Americans are regarded as having some sort of physical disability. New materials and both functional and anatomical modeling based on magnetic resonance imaging and computed tomography have brought much relief to such individuals.

HOW IT WORKS

SPARTA begins designing each orthotic or implant by selecting appropriate composite thermoset and thermoplastic compounds for the application, including those that are formable at low temperatures, lightweight, and low cost. Then it selects the length of the fibers. SPARTA's technology combines the best of continuous and chopped fibers, which provides the necessary formability yet retains the high strength of the materials. These materials can also be constructed for stiffness without malleability when needed, as in the ankle joints, knee joints, and foot plates.

MEDICAL SIGNIFICANCE

SPARTA's technology is especially useful when strong, lightweight materials are needed for full-leg braces, ankle joints, knee joints, foot plates, hip implants, bone implants, and spinal implants. External bracing is designed primarily for patients who have lower-extremity paralysis after spinal cord injury, with some limited applications for post-polio syndrome and congenital disorders. Composite orthopedic implants for repairing long-bone fractures and stabilizing spines are also under study.

The medical community's interest encouraged SPARTA to develop implantable biomimetic components, including femur and spinal implants. SPARTA—with the National Science Foundation; the University of California at Davis; Mekanika, Inc. (Miami, FL); the University of Miami, Department of Orthopedics; and Brent Adamson, M.D., (Kearney, NE)—studied repairing long-bone fractures with composite devices. The study used a composite femur implant for testing because of the strength required and the large amount of readily available data on steel implants. The information, methods, and synthetic materials used in the composite femur implant are also applicable to other long bones.

SPARTA, in a joint venture with Mekanika, is developing a spinal implant to immobilize vertebrae and has worked with the Defense Advanced Research Projects Agency to generate Food and Drug Administration data and commercialize the spinal implant. Mechanical testing is continuing along with cadaver studies. SPARTA is now working on testing the complete system, rather than the individual components, and is directing its energies to lowering the system cost.

VENTURES OR PRODUCT AVAILABILITY

SPARTA has worked with the National Rehabilitation Hospital (NRH; Washington, DC), the General Reinsurance Corporation, and Becker Orthopedic Appliance Company (Troy, MI) to develop lightweight knee and ankle joints. In particular, this effort resulted in an articulating drop-lock knee joint that can be either locked in the upright position for walking or unlocked for sitting, allowing the leg to bend. Both joints passed mechanical static and fatigue testing. The knee joint is in clinical trials, and the ankle joint is now in clinical evaluation at NRH. SPARTA has met its goal of reducing materials costs for the ankle joint.

The National Institutes of Health (NIH) is in discussion with SPARTA and the inventors of the "Seattle foot" for a prosthetic study. The Seattle foot is notable for its appearance in television advertisements in which double amputees play basketball. Currently, this venture is on hold because of SPARTA's transformation from small business to large, which makes it ineligible for NIH Phase II SBIR funding. Proof of concept was successfully demonstrated under a Phase I SBIR contract.

SPARTA's program manager for bioengineering of advanced material products is Moreno White, whose awards for bioengineering include the 1989 SDIO/ADPA Technology Transfer Award, the 1993 DuPont/ASM Composite Systems Award for the composite leg brace, and the 1996 Composites Institute's Award of Excellence.

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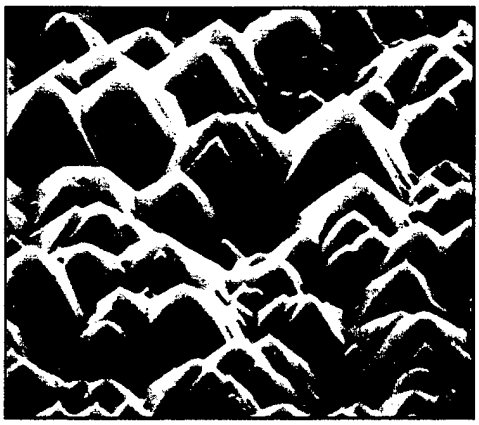
SPIRE'S ION-BEAM APPLICATIONS

BMDO HISTORY

With the help of BMDO SBIR contracts, Spire Corporation (Bedford, MA) developed an ion-beam texturization method that can create intricate surfaces on a variety of materials. For BMDO's Advanced Optical Baffles program, Spire used its patented SPI-TEXT method to create random patterns on optical sensors that aid in rejecting stray light. These sensors were used in BMDO's moon-orbiting spacecraft, Clementine, as part of the light collection system for star tracking. The same texturization method plays an integral role in Spire's biomaterial product line.



SPI-TEXT creates random patterns on surfaces that can be useful for many biomaterials.

Bacterial endocarditis is an infrequent complication of valve replacement surgery, but once acquired it can be fatal to nearly 60 percent of patients. It can also be acquired by rheumatic heart patients after simple surgery or dental procedures. In both cases it can usually be prevented with antibiotics.

HOW IT WORKS

Spire developed an advanced surface modification technology based on ion-beam implantation and ion-beam-assisted deposition techniques. To produce optically dark surfaces, metals are bombarded with ions to create micrometer-scale textures, increasing surface area and providing light-trapping pores. For biomaterials that are either polymeric or metallic, this etching can alter surfaces for all manner of applications—for example, providing better anchoring for bacteria in petri dishes or, conversely, by coating and smoothing a catheter surface to prevent bacterial adherence.

MEDICAL SIGNIFICANCE

While medical procedures certainly save lives and alleviate suffering, many of the physical invasions associated with modern practices automatically introduce new problems. Any device that is inserted into the body carries with it a threat of infection. Bacteria are often particularly attracted to polymers in portions of hip and knee implants, as well as indwelling catheters and heart valve sewing cuffs. They easily take up residence on these devices in a resistant covering called a biofilm. Even bacteria that are normally eradicable by antibiotics can avoid harm by colonizing implants in this manner. In addition, rough surfaces on medical devices can promote the formation of clots that can travel to the lung, heart, and brain, with devastating consequences.

One of Spire's latest efforts has been in impregnating replacement heart valve sewing cuffs with silver metal through an ion-beam process called SPI-ARGENT. This coating of elemental metal helps prevent bacterial

growth on the cuff, thus lowering the incidence of postreplacement endocarditis, a life-threatening infection of the heart's inner lining. In early June 1997, Spire announced an exclusive agreement with St. Jude Medical, Inc., to develop the heart-valve sewing cuff. St. Jude produces mechanical heart valves that are considered the gold standard in the industry. Using related technology, Spire also treats central venous catheters and surgical guide wires to reduce the likelihood of clot formation and increase lubricity, which eases the insertion process.

VENTURES OR PRODUCT AVAILABILITY

Spire's registered and trademarked techniques include the following:

IONGUARD enhances the mechanical and chemical surface properties of titanium alloy, cobalt-chromium, and other metal and ceramic orthopedic or dental devices. Overall, this process makes artificial joints more durable by increasing wettability and reducing friction; it also enhances adhesion to biocompatible cements.

SPI-TEXT texturizes electrodes used in cardiac pacemaker batteries. The increased surface area improves tissue attachment and decreases electrical resistance at the contacts. Testing showed that battery lifetimes were increased by 300 percent, electrode resistance was reduced, and battery weight was decreased. SPI-TEXT was licensed by a cardiac pacemaker manufacturer in 1993.

SPI-ARGENT treats polymer, metal, and ceramic medical devices to reduce the material's ability to induce blood clotting (increase thromboresistance), to reduce bacterial adhesion, and to improve hardness, slickness, and bondability of surfaces.

Spire's recently introduced line of central venous catheters is treated with a process called SPI-POLYMER. The process is designed to create a slick and thromboresistant surface for catheters.

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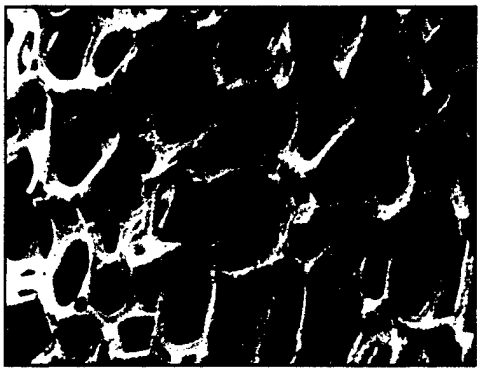
NOVEL MATERIAL FOR SPINAL IMPLANTS

BMDO HISTORY

Ultramet (Pacoima, CA) received SBIR funding from BMDO to develop insulator materials for rocket nozzles. From this research, the company successfully manufactured synthetic cellular foams that can serve both as insulators and as kinetic energy absorbers. The foams are made of ceramic, metal, and glass and can be used for biomedical, environmental, and construction applications.



Ultramet's synthetic cellular materials are readily compatible with natural bone.

In evolutionary terms, the human spine is an imperfect support system because of our fairly recent adaptation to the upright position. It was really designed for creatures who move on all fours. Back pain and spinal disorders are prevalent in human lives, largely because of this engineering glitch.

HOW IT WORKS

Ultramet's materials are composed of a carbon foam skeleton that is treated by a chemical vapor deposition (CVD) method to lay down a coating of various compounds and elements. Through CVD, a continuous thin film of metals such as rhenium or tantalum, or compounds such as silicon carbide, can be distributed throughout the interior of the construct, lending certain thermal or tensile properties to the carbon foam substrate and to the structure as a whole. The resulting products are characterized by low cost, low density, high chemical purity, controlled thermal expansion, and high thermal stability. Depending on the coating used, the material can be made resistant to oxidation and can withstand temperatures of up to 6,000° F. The high strength and porous structure of one Ultramet product, Hedrocel®, makes it especially useful as a biocompatible replacement for the vertebral bodies that make up the spinal column. Hedrocel is a tantalum-coated carbon porous matrix product that mimics the properties of, and is compatible with, bone.

MEDICAL SIGNIFICANCE

The problems of the aging spine can be traced, at times, to loss of soft tissue between the vertebrae. This can lead to pain from compressed spinal nerves. Cancer that has metastasized to the spine, degenerative diseases such as arthritis, and trauma can also compromise soft tissue. Hedrocel was licensed by Implex Corporation (Allendale, NJ) to be used in replacement discs for the spinal column. Specifically, the replacement acts as a spacer in support of the vertebral body, or the round portion of the disc. The porous natural structure of bone is simulated by Hedrocel, and bone can gradually infiltrate into the artificial disc just as it would into a dam-

aged section of natural bone. The vertebral body implant is screwed into place, sometimes with a cement accompaniment, and consolidation takes place as the bone and Hedrocel implant fuse together. The fusion obviates the necessity for the soft tissue disc, and the two bony processes grow together, reducing the possibility of nerve compression and therefore pain.

VENTURES OR PRODUCT AVAILABILITY

Early animal studies funded by the National Institutes of Health spurred Implex to build facilities specifically for Hedrocel implant products. Hedrocel vertebral implants were then used in eight European patients in late 1994. They are currently being used in a United Kingdom trial of 25 patients, specifically for replacement of the lower cervical vertebrae. Implex is also planning to manufacture devices for the small joints of the fingers, as well as components for hip replacements.

Ultramet owns the patent on the carbon foam process. Ultramet licensed the technology to Implex, which trademarked Hedrocel.

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SECTION B
TREATMENT

Lasers have found their way into medicine, replacing scalpels in some cases, augmenting drug-tissue interactions, reducing discomfort in dental procedures, and reshaping the surface of the eye. Based on funding from BMDO's Medical Free Electron Laser (MFEL) program in the mid-1980s through the early 1990s, photomedicine became a true specialty. In 1996, the first photodynamic therapy drug, Photofrin, was approved for the treatment of esophageal cancer. This drug, its cognates, and second-generation derivatives were studied in depth at a number of clinical centers and universities, thanks in large part to the MFEL program. Also represented here is a sterilization method for liquid and solid foods, a timely subject in light of the recent rash of food- and water-borne illness in the United States.

1. Two world-recognized facilities that perform state-of-the-art photomedical research and provide clinical treatments for skin disorders and cancer and develop laser-based imaging technologies.

2. New collagen-bonding treatments for joint disorders and improved outcomes for lens replacement surgery.

3. A "cool" sterilization technology that kills deadly *Cryptosporidium* and leaves foods and liquids unaltered.

4. New laser therapy for effective cavity prevention and practically painless root canal treatment.

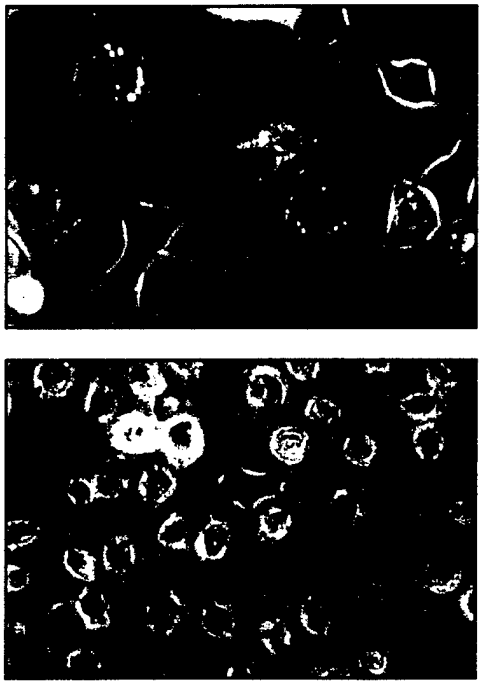
5. Ultrafast switches for lasers, electroporation devices, and a novel tomographic imaging technique.

WELLMAN LABORATORIES OF PHOTOMEDICINE

BMDO HISTORY

During the late 1980s, BMDO funded the MFEL program to allow medicine to leverage the Defense Department's advanced laser technology. With help from this initiative, Massachusetts General Hospital (Boston, MA) nurtured a combined research and clinical laboratory that came to be known as the Wellman Laboratories of Photomedicine. In this brief period, Wellman has achieved worldwide recognition for its excellence in light-based medicine, as well as a pioneering milestone in cancer treatment called photodynamic therapy. Thus, technology transfer from the high-powered free electron laser, originally conceived to kill enemy missiles, has enabled destruction of a different sort.

Lasers have revolutionized the lucrative practice of cosmetic surgery and related services. For depilation alone, where lasers have just made an entry, the U.S. market is estimated at $1 billion.



Photodynamic therapy can selectively destroy cancerous cells.

HOW IT WORKS

The discrete wavelengths and short, well-controlled pulses of laser devices allow clinicians to investigate and observe specific physical interactions. For instance, certain skin pigments such as melanin absorb light at a particular wavelength, as does the hemoglobin in red blood cells. Researchers can take advantage of these particular traits and tailor new therapies to old disorders. The MFEL program allowed researchers access to powerful free electron lasers, which in turn led to insights for new applications of Nd:YAG, carbon dioxide, and other medically useful lasers.

MEDICAL SIGNIFICANCE

Photodynamic Therapy. Wellman Laboratories of Photomedicine has developed a wide range of light-based therapies. The most notable among these is photodynamic therapy (PDT), a method of killing tumors and other diseased tissues that has been approved by the Food and Drug Administration (FDA). Lasers are a critical part of PDT because a precise wavelength of light is needed to activate the tumoricidal drug. In this case, the drug is Photofrin, a compound that is preferentially absorbed by cancer cells. The drug remains inactive until exposed to light, whereupon it releases high-energy oxidation products that kill the tumor, in a manner similar to how the immune system eliminates damaged or diseased cells. Normal tissue is spared, and there are few undesirable side effects. Second-generation photoactive drugs such as benzoporphyrin derivative are also being tested for efficacy in PDT, and the applications are not limited to cancer. Rheumatoid arthritis, psoriasis, endometriosis, macular degeneration, and regrowth of arterial plaque after angioplasty are all conditions that are being treated experimentally with PDT.

Laser Treatment of Skin Lesions. Before lasers were accepted as a clinical tool, pigmented skin lesions such as the purplish-red port-wine stain and the common hemangioma, or "strawberry mark," were not satisfactorily

treatable. Lesions that appear on the face are cosmetically disturbing to the patient, and occasionally a hemangioma can threaten eyesight or obstruct the nose or mouth. Researchers at Wellman have achieved truly remarkable results with laser treatment of these lesions. Copper vapor lasers and Nd:YAG lasers are used to deliver a 585-nanometer laser beam to the affected area. After repeated treatments, the red pigment (from hemoglobin mostly) fades away, and the normal color of the skin emerges.

In a related therapy, superficial capillaries, or spider veins, can also be treated with lasers. Wellman uses a 595-nanometer laser to obliterate these unsightly but usually harmless veins. The alternative treatment, called sclerotherapy, involves injection of saline solution or other sclerosing compound that collapses the blood vessel walls. Sclerotherapy can be painful and can result in discoloration that is more objectionable than the original condition. For cosmetic concerns of another sort, Wellman is also developing a method of laser depilation, similar to a technique that is now on the market. The difference in Wellman's technique is that the laser is used without preapplication of a light-absorbing lotion. Thus far, studies have shown that the laser method can prevent hair regrowth for up to 31 weeks.

Laser-Induced Fluorescence of Cancerous Lesions. Laser-induced fluorescence spectroscopy has become an exciting window into the cell. Precise wavelengths induce precise excitations, and cancerous lesions can be seen as bright spots that can be well distinguished from their normal surroundings. In endoscopically accessible regions of the body, such as the bladder, esophagus, and lungs, a fiber-optic probe can deliver laser light and then transmit the fluorescence response to a spectrometer, which analyzes the returning light. At Wellman, doctors are using this technique to inspect the bladder wall in order to distinguish cancerous lesions from normal tissue. After comparing unique fluorescence patterns, a false-color imager can show the doctor a well-defined picture of the tumor, allowing successful excision and avoiding surgical damage to the nondiseased portion of the bladder.

VENTURES OR PRODUCT AVAILABILITY

Wellman continues to develop and implement novel treatments involving the use of light and photochemicals. Approximately $250 million in commercial revenues have been generated by the laboratory's photomedicine activities, mostly through sales of medical lasers.

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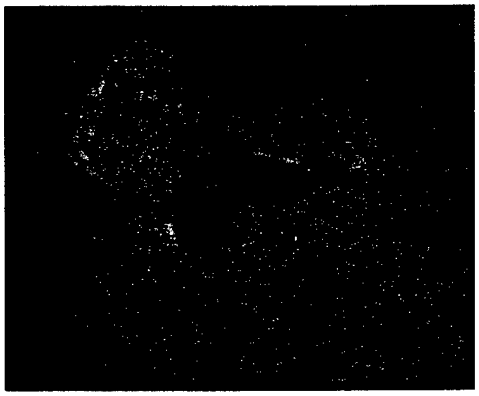
BECKMAN LASER INSTITUTE ADVANCES



Beckman's researchers use "laser tweezers" to isolate and examine single cells.

BMDO HISTORY

Along with other centers of excellence such as Stanford and Baylor Research Institute, the Beckman Laser Institute (BLI; Irvine, CA) received funding through the MFEL program. Like the Wellman Laboratories of Photomedicine (Boston, MA), this institute has made many advances in photomedicine in areas such as photodynamic therapy (PDT) and laser treatment of dermatologic diseases. BLI was established in 1982 as an international center for laser studies and includes a medical clinic that functions as an outpatient facility of the Medical School of the University of California at Irvine. Other areas of interest include treatment of cataracts, glaucoma, and gynecological conditions, and novel imaging modalities.

Recent in vitro studies suggest that low-level ultrasound can be used in place of light to activate PDT drugs. An advantage of this approach would be to eliminate invasive fiber-optic light delivery systems and laparoscopic access to internal structures.

HOW IT WORKS

Most living tissues exhibit some wavelength-dependent absorption, reflection, and transmission. By taking advantage of these discrete differences in laser-matter behavior, researchers can tailor laser-beam wavelengths to a particular target without harming surrounding tissue. The laser-matter interaction can be direct or can be assisted with drugs that are preferentially absorbed by a target tissue.

In addition to treating diseases, laser light energy can be used to create optical traps and to cut cellular components. "Laser tweezers" and "laser scissors" are now becoming a recognized part of the biological tool kit. Laser transmission, reflectance, and scatter through tissue can also be used to create both macroscopic and microscopic images and to collect data for spectral analysis.

MEDICAL SIGNIFICANCE

Photodynamic Therapy. PDT will very likely be adapted as a regular part of the cancer treatment pharmacopoeia in short order. For reasons not yet well understood, abnormal tissues collect the photosensitive drug preferentially, while normal tissues collect far less. When light of a specific wavelength is applied to the treated area, a toxic oxidative reaction takes place. The reaction kills tumor cells but spares normal tissue—a "surgical strike" without surgery. So far, PDT has shown itself to be generally nontoxic to healthy tissues when compared with conventional chemotherapy, which damages all tissue. PDT also seems not to encourage drug resistance, a problem that frequently occurs in repeated cancer treatments. A recently approved drug, Photofrin, is part of a newly FDA-approved PDT regimen (currently limited to end-stage esophageal cancer) and is just one of the drugs being tested at BLI. The institute's researchers are using a number of PDT protocols, along with second-generation PDT compounds, to treat cancers and gynecological disorders.

Novel Imaging Device. Bruce Tromberg, Ph.D., and a group of medical researchers at BLI have developed a fast, portable near-infrared spectrometer to probe for tissue abnormalities, such as breast tumors. The optical device uses a new optical imaging modality, called frequency-domain pho-

ton migration, which is safe, noninvasive, inexpensive, and potentially more sensitive and accurate than other imaging techniques.

To detect abnormal breast tissue, the handheld laser diode instrument sends near-infrared light through the tissue to determine its optical properties. As light propagates through tissue, the researchers measure how many photons were scattered or absorbed. These data can then be interpreted to yield tissue hemoglobin levels, blood volume, and water content. With this information, certain diagnoses can be made.

For example, a great deal of scattering might signal high cell density, a sign of cancer. Malignant tumors also may absorb more light because they contain more hemoglobin than normal tissue. Fluid-filled cysts should have lower than usual scattering, because the density of fluid is lower than that of normal tissue.

Laser Tweezers and Scissors. Beckman's director, Michael Berns, Ph.D., and Tromberg have collaborated to develop devices such as laser tweezers and scissors that can be used to immobilize and manipulate cells and their contents. Berns's early interest in chromosome cutting has led to the ability to optically cut lengths of DNA and selectively amplify these sequences. Currently, molecular biologists use a variety of wet chemistry techniques to enzymatically cut DNA (with restriction endonucleases derived from microbes). The laser scissors device, if cost-effective, is a cleaner, more direct alternative to endonuclease cutting; moreover, restriction endonucleases can be used at only a limited set of four- to eight-nucleotide sequences in the genome. The laser tweezer, scissors, and the free electron laser based microscope are basic research tools at present.

VENTURES OR PRODUCT AVAILABILITY

Photofrin, manufactured by QLT Photopharmaceuticals (Vancouver, BC) was approved for treating late-stage esophageal cancer in late 1996 and is being used in a number of clinical centers, including BLI, for PDT. PDT for noncancerous conditions such as endometrial hyperplasia is also being assessed, as well as novel photosensitive drugs.

Through a collaboration with the Chao Family Clinical Cancer Research Center (Orange, CA), Tromberg is testing the tissue spectrometer's ability to differentiate between normal and abnormal tissue. He and John Butler, M.D., have gathered and analyzed data on about 30 patients. The researchers are now correlating these data to such conventional techniques as mammography and histopathology.

Tromberg says that the results look promising at this point: the data correctly predicted a fluid-filled cyst in one patient and a fibrous tumor in another. He anticipates more extensive clinical trials within two years. Ultimately, he hopes the research will result in a needle-free breast cancer detection device to complement, not replace, mammography. Tromberg's team received a patent for frequency-domain photon migration in 1992.

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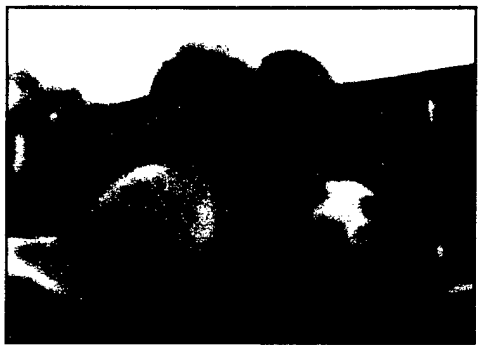
BAYLOR PHOTOSENSITIZING AGENTS



Baylor has a new drug that can help maintain vision clarity in lens replacement patients.

BMDO HISTORY

In the early to mid-1980s, BMDO supported the MFEL program, designed to transfer military expertise in laser development to the medical sector. Baylor Institute (Dallas, TX) was just one recipient of MFEL funding. Large, expensive free electron lasers were not (and indeed are still not) commonly available, and the biological benefits of the lasers' broad wavelength range were therefore hard to realize. The MFEL program offered medical scientists a chance to use the lasers' versatile characteristics, and attendant observations of tissue-wavelength interactions, to further develop their hypotheses. A very large number of clinically significant outcomes resulted from this collaboration. Among them were the development of photosensitive agents that can be used in treating cataracts and even cancers.

Approximately 40,000 corneal transplants are performed every year on an outpatient basis under local anesthetic.

HOW IT WORKS

The wide wavelength range afforded by free electron lasers helped researchers explore a greater variety and more discrete assortment of laser energies and frequencies. Most materials, including biological tissues, absorb light markedly well at a certain wavelength, while handily reflecting light at others. Hemoglobin, for instance, absorbs very strongly at between 580 and 600 nanometers, corresponding to the green-yellow part of the spectrum. For this reason, laser therapy of hemoglobin-rich birthmarks such as port-wine stains has found resounding success in recent years. The hemoglobin, and not the surrounding healthy skin, absorbs the intense energy of the coherent light, and the unsightly red marks break down and fade. Similarly, other cellular components react in predictable ways when they absorb light, and through the activity of photochemicals, they can be targeted by light activation.

MEDICAL SIGNIFICANCE

The latest advances at Baylor include a photochemical method of removing tumor cells from bone marrow in preparation for autologous transplant. In patients who have a relapse following chemotherapy for cancer, a more vigorous and potentially toxic chemotherapy protocol is now used. To prevent irreparable damage to the marrow stem cells, the marrow is removed and stored while the patient undergoes therapy. Baylor researchers are studying the use of photochemicals and light on the marrow cells as a means of ensuring that the marrow will be purged of any residual tumor cells. Thus when the marrow is returned to the patient to reconstitute the blood and immune system, the danger of cancer recurrence is reduced. Other chemical methods of purifying marrow stem cells kill about 80 percent of the stem

cells. The photochemical method preserves 80 percent of the stem cells. It is projected that a larger number of surviving stem cells will increase the likelihood of a successful take of the cells upon transplantation.

Researchers at Baylor have also developed a photochemical treatment for cataract patients. Cataracts, or proteinaceous growths on the lens of the eye, can obscure vision to the point of blindness. Lenses can be replaced with surgery, but 30 percent of patients experience exuberant regrowth of tissue over the lens as a result of an overactive healing process. A new surgical adjunct method uses naphthalimide dye and blue laser light to treat the capsule, or lens implant site, before placement of the new artificial lens. This intervention reduces tissue regrowth that can obscure the new lens.

A novel photoactive dye that inhibits the activity of collagenase and links adjacent collagen fibrils together is also under investigation. Collagen is a fibrous protein that serves as a connecting and supporting structure in connective tissues throughout the body. Collagen is the primary protein found in the tendons, ligaments, bone, cartilage, skin, organ capsules, and cornea and sclera (white) of the eye. During tissue remodeling and following trauma, collagenase, an enzyme that disrupts the bonds between collagen strands, is released to digest the collagen. The photochemical bonding is achieved by painting a photochemical on a damaged surface of a torn tissue, such as the cartilage meniscus in the knee joint or a torn surface of a cornea, and then exposing these surfaces to a blue laser light. This causes the formation of new bonds between adjacent collagen fibrils and also makes them resistant to further degradation by collagenase. This new approach to tissue bonding offers a sutureless system that is more efficient at healing the treated surface.

VENTURES OR PRODUCT AVAILABILITY

The ophthalmology applications are being investigated further in a joint effort between Baylor researchers and investigators at the Kansas Eye Institute. Additional studies on the toxicity and metabolism of the photochemicals are in progress to enable clinical testing of the stem cell procedure and collagen bonding procedure in humans. Work on the collagen linking was partly supported by the MFEL program and the Arthritis Foundation. Patents on the dye synthesis and applications are issued to the inventors.

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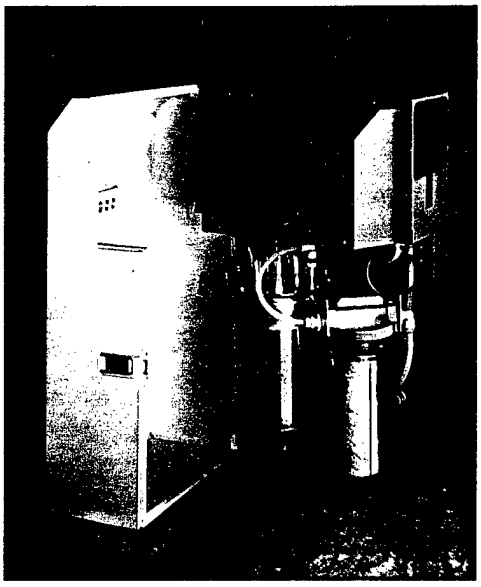
HIGH-ENERGY CAPACITORS TO HELP ZAP MICROBES



PurePulse has introduced a fast and effective method for eliminating deadly bacteria, viruses, and other microorganisms.

A major outbreak of waterborne *Cryptosporidium* occurred in the summer of 1993, sickening about 400,000 people in the Milwaukee area. There is no effective treatment for this parasite, which can also be spread through foods, juices, and personal contact. Water filtering and hand washing are good preventive measures.

BMDO HISTORY

PurePulse Technologies, Inc., a subsidiary of Maxwell Technologies (San Diego, CA), has developed a highly efficient FDA-approved method for killing parasites, bacteria, and viruses in water, on the surfaces of medical and food packaging, and in liquid foods. Dubbed PureBright® and CoolPure®, the two systems deliver, respectively, microsecond bursts of intense light or a pulsed electric field to rupture the membranes of pathogenic microbes. Based on advanced high-energy capacitors, the systems offer kill rates 100 to 10,000 times those of conventional mercury lamp ultraviolet treatments. BMDO partially funded development of these capacitors to produce a compact, lightweight device that could provide pulsed power for space-based lasers and accelerators.

HOW IT WORKS

Capacitors accumulate electrical charge and energy on the surfaces of conducting plates that are insulated from each other by a dielectric material. Maxwell developed its capacitors by using insulating materials with a higher dielectric constant, reducing the thickness of the insulating material, increasing the voltage between the conductors, and reducing the thickness of the conducting plates. Through this combination, Maxwell successfully produced its high-density thin-film capacitors, which have been used to power implantable cardiac fibrillators. PurePulse used this same technology to develop its purification systems.

MEDICAL SIGNIFICANCE

PureBright has been shown to kill the deadly *Cryptosporidium*, a recently resurgent pathogen in municipal water systems. Moreover, the organism is killed in the oocyst phase, a particularly resistant stage in its life cycle. Viruses are also eliminated by the system. PureBright is designed to treat clear fluids, but it also effectively kills bacteria, mold spores, and viruses in air ducts and on filter surfaces. Used with ultraviolet-transmissive polymers such as polypropylene or polyethylene, PureBright can also sterilize saline solutions in intravenous bags, making sterilization a one-step process. Other applications include sterilizing packaged foods, decontam-

inating cup and lid packaging, and treating fresh meats, fruits, and vegetables to prevent microbial degradation and eliminate contamination.

CoolPure preserves opaque liquids such as milk, soups, and juices without heating and therefore without denaturing the treated product. As most people are accustomed to the flavor of heat-pasteurized milk, they may find CoolPure-treated raw milk an acquired taste. However, retention of raw milk components such as rennin, the curdling enzyme, is important for cheese production. CoolPure is bactericidal at temperatures from 25°F to 60°F and is designed to treat pumped liquids as they are flowing. The quick treatment time ensures an acceptable product flow rate. CoolPure may also enhance the yields of some pharmaceutical and biotechnical processes.

VENTURES OR PRODUCT AVAILABILITY

PurePulse is in discussion with leading medical manufacturers for various sterilization applications. The company has contracted with a large international fast-food chain for decontaminating water, the U.S. Army for sterilizing food, and a manufacturer for treating liquid whole eggs. PurePulse configures its systems to the user's needs and welcomes inquiries.

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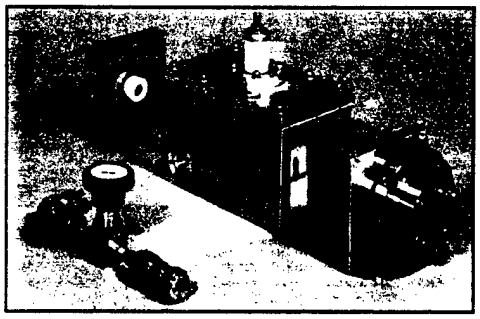
CARBON DIOXIDE LASERS FOR MEDICAL APPLICATIONS



QSource's air-cooled lasers are poised to enter the medical and dental markets.

BMDO HISTORY

QSource, Inc. (East Hartford, CT), received both Phase I and II SBIR funding for building compact, lightweight carbon dioxide (CO_2) lasers for LADAR systems. In 1996, QSource won a Phase II contract through the new SBIR Fast Track program, with Medical Optics, Inc. (MOI; Carlsbad, CA), providing the matching funds.

Although a third of today's youngsters between 5 and 17 are cavity free, tooth decay remains second only to the common cold in disease prevalence.

HOW IT WORKS

QSource has licensed its radiofrequency, direct-current (RF-DC) CO_2 laser to MOI for medical and dental applications. Dental applications are one of the initial target markets for QSource's modular laser technology, which also has good industrial potential. In addition, these lasers are suitable for existent and emerging soft-tissue medical treatments, such as laser skin resurfacing.

QSource's sealed, air-cooled CO_2 laser is a modular, repetitively pulsed instrument that employs a sealed tube configuration and a hybrid RF-DC electrical discharge lasing mechanism. The design's advantages are system reliability, ease of maintenance, and device life over conventional CO_2 lasers. The design makes possible less costly manufacturing methods in production. It achieves high power output with its combined RF-DC excitation mode, which produces peak pulsed power levels (as high as 1 kilowatt) several orders of magnitude higher than the average output power. The sealed design also allows system flexibility and portability, since the laser need not be connected to an umbilical gas line. It can also operate in a continuous-wave mode and boasts a lifetime of more than 1,000 hours in the product configuration.

MEDICAL SIGNIFICANCE

CO_2 lasers are already in widespread use in the medical realm, and with the pulsed power capability of QSource's design, these lasers have promising dental applications. In MOI-sponsored research at the University of California at San Francisco Dental School, 9.3-micrometer-wavelength laser pulses are being investigated as a way to seal tooth enamel and inhibit dental caries (cavities). Studies suggest that rapid pulsing of teeth can make them five times more resistant to caries formation, and in some cases, the laser treatment can even remineralize areas of incipient decay. The brief treatment is less time-consuming than fluoride treatment (which can discolor teeth) and polymer sealant application.

Another significant research area is laser pulpotomy, or laser treatment of dental pulp, the vital portion of the tooth. At Beckman Laser Institute (Irvine, CA), MOI's CO_2 lasers (also designed with QSource technology) are being used in dogs to treat pulp infections. The laser method removes inflamed tissue before infection can destroy the whole tooth, and it leaves healthy tissue intact so that the tooth remains functional and retains its living root. The method may become an alternative to root canal therapy, a painful procedure that millions of human patients undergo each year. Unlike the forceful physical debridement methods of conventional root canal therapy, laser treatment is expected to result in better tooth retention and reduced future complications.

VENTURES OR PRODUCT AVAILABILITY

David Nielsen, D.V.M., a Manhattan Beach, CA, veterinarian, has been using the CO_2 laser in his canine dental practice since 1995. He works in collaboration with Petra Wilder-Smith, D.V.M., and George Peavy, D.V.M., of the Beckman Laser Institute. Documentation of this work will eventually be used to justify human trials.

MOI, a subsidiary of Kaiser Aerospace and Electronics, has agreed to provide matching funds for technology development in the Fast Track Phase II agreement, the total of which amounts to $1 million over two years. MOI sponsors research at the University of California at San Francisco in dental applications and plans to market QSource technology for the many procedures that the FDA has already approved for CO_2 lasers.

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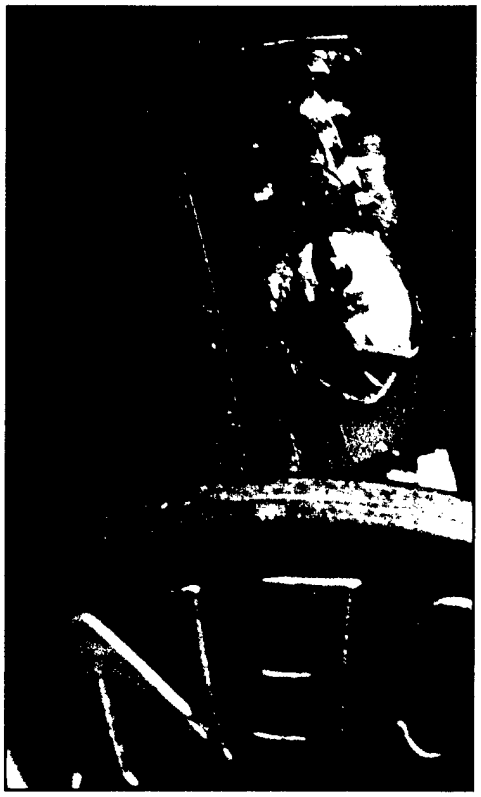
ULTRAFAST LIGHT-ACTIVATED SWITCHES



The minuscule silicon switch has multiple applications in biotechnology and medical imaging.

Electroporation is now a workhorse application for molecular biology, where it is used to transform bacteria, yeast, and human cells with foreign DNA, enabling *E. coli*, for instance, to secrete mammalian proteins like insulin or interferon.

BMDO HISTORY

Energy Compression Research (ECR; San Diego, CA) has developed a revolutionary ultrafast semiconductor switching technology called light-activated silicon switching (LASS). With contracts from the early days of BMDO research, ECR focused its efforts on developing photoconductive switches that have applications in electronics, electro-optics, and photonics for weapons such as the electromagnetic gun.

HOW IT WORKS

ECR's LASS technology involves semiconductor devices that use laser light to switch a current on or off. Semiconductors are ubiquitous in the electronics industry, where they function as power amplifiers, storage modules, and switches. Switching current on and off is the most general function of the semiconductor. Conventional semiconductor switching time is governed by the speed at which electrons traverse the switch. The LASS device uses the absorption of laser light to create the conducting electrons within the semiconductor, resulting in a thousandfold increase in switching time compared with conventional switches. The high-speed, low-jitter, and zero-delay LASS device can be used to power lasers, route signals in fiber-optic communications devices, control industrial motors, and power high-frequency radar communications. LASS technology offers high efficiency and cost savings in these areas.

MEDICAL SIGNIFICANCE

ECR is currently developing LASS technology for applications in the medical industry. One area of concentration includes analytical instruments such as flow cytometers, mass spectrometers, and fluorescence lifetime spectrometers. Lasers designed by ECR provide high reliability as well as a compact footprint for these devices.

A second medical application is in imaging systems. ECR is looking to the far-future application of optical diffuse tomography, a technology that may enable doctors to perform mammography without ionizing radiation. This technology was envisioned more than a generation ago as "diaphanography," a method that is familiar to anyone who has shone a flashlight through his or her hand. For breast tissue, however, high-intensity visible-

to-infrared light is necessary for penetration and visualization, and a means of optical gating must be used to reconstruct the image. Technologies such as LASS devices and better understanding of the optical properties of living tissue are stimulating interest in this field.

ECR lasers offer well-defined short pulses with high repetition rates for surgery, particularly eye surgery.

In electroporation, an intense short pulse of electricity is used to provide the force that opens cellular pores, enabling the insertion of macromolecules like DNA into cells of interest. It is a commonly used method for basic research in biology and for "transfecting" cells in genetic studies. However, many cells are sacrificed in the process; up to 50 percent are destroyed when using a DC power source to induce pore formation. LASS technology can reduce cell loss to 10 percent by using a square-wave pulse to effect rapid and reversible pore formation.

VENTURES OR PRODUCT AVAILABILITY

ECR manufactures microlasers, fast Pockels cell drivers, and laser diode drivers. The microlaser series is an established commercial product that is distributed worldwide. Microlasers are being used in temperature sensor systems, scientific instruments, and a broad range of product development areas, including biomedical, electrical utility, micromachining, and defense systems.

The Pockels cell driver is also a commercial product that uses ECR's LASS technology as the heart of the system. It is used in a variety of lasers and switches at megawatt power levels and picosecond speeds.

ECR also manufactures and distributes solid-state, high-current pulse generators designed to drive laser diodes. Applications include biomedical sensors, fiber-optic systems, and LIDAR measurements. Several new products incorporating LASS technology are under development and are planned for release in the coming year.

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he editor wishes to dedicate this report to Lee W. Rivers, who helped develop U.S. technology transfer policy by Executive Order during the Reagan Administration. He has also served as an Executive Director of the National Technology Transfer Center in Wheeling, W V, a board member of the Association of Federal Technology Transfer Executives, and an officer of the Technology Transfer Society.